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Original Communications

STUDIES IN MITRAL STENOSIS. II. OBSERVATIONS ON INCIDENCE OF ACTIVE RHEUMATIC CARDITIS IN LEFT AURICULAR APPENDAGES RESECTED AT OPERATION FOR MITRAL STENOSIS

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THE DETECTION of latent rheumatic activity in cases of rheumatic heart disease without active rheumatic manifestations is, in the present era of active surgical treatment, of great practical importance. It is generally agreed by those who work in this field[1-4] that active rheumatic carditis is a contraindication to operation and that operative procedures should be postponed until the situation has cleared. This is unquestionable in cases of acute endocarditis, myocarditis, or pericarditis. Sometimes, however, there may be considerable doubt whether an active process is present or not. We have then chosen to observe the patients carefully over a long period before making any positive decision as to operation.

All patients with mitral stenosis, who are accepted for study with regard to the possibility of surgical intervention, undergo, as a routine procedure, certain laboratory tests in order to disclose possible rheumatic activity or subacute bacterial endocarditis. These tests include: erythrocyte sedimentation rate (ESR) according to Westergren, blood culture, antistreptolysin titer (ASL), and agglutination of sensitized erythrocytes (ASE).

Whether rheumatic activity was present or not was judged from the results of these tests as well as from a detailed history, physical examination, temperature chart, and electrocardiogram. In Table I, data are given for the eighteen patients operated upon so far. As an expression of possible electrocardiographic signs of rheumatic activity, the P-Q intervals were recorded in conformity with a common practice. (We do not, however, attach much importance to prolonged P-Q intervals in these cases as all patients were well digitalized.) Data are also given in every case on the age at which the diagnosis of the rheumatic activity and of the valvular lesion was first made. The surgeon's impression of the type of mitral valve is also reported.

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TABLE I

NAME	AGE (YRS.)	AGE AT FIRST DIAGNOSIS		P-Q	ESR	ASL	ASE	VALVULAR TYPE	ENDOCARDIUM		
		RHF	V.H.D.						RECENT THROMBOSIS	ORGANIZED THROMBOSIS	FIBROSIS
S. N.*	24	?	9	*0.22*	2	125	20	Membranous	—	+	(+)
R. M.	34	?	29	0.17	12	125	0	Membranous	—	—	(+)
S. K.	30	?	24	0.16	3	*250*	0	Membranous	—	—	(+)
B. O.	33	?	23	A.F.	*87*	125	0	—	—	++	(+)
E. A.	44	18	39	A.F.	14	110	0	Calcified	—	?	+
M. N.	26	13	18	A.F.	5	125	0	Muscular	—	++	—
E. B.	44	?	39	*0.24*	14	*250*	10	Membranous	—	—	(+)
V. L.	33	23	24	0.20 *A-VBII*	14	125	0	Membranous	+	—	(+)
E. S.	51	?	17	0.19	17	—	—	Very fibrotic	—	(+)	—
E. R.	41	21	33	0.19	*47*	720 125 *250*	0	Membranous	—	—	(+)
A. P.	41	28	40	0.20	8	110	0	Slight fibrosis	—	—	+
M. Ö.	35	?	34	0.15	6	125	0	Very fibrotic	—	—	+
S. H.	28	9	9	0.17	13	150	0	Fibrotic	—	+	—
H. N.	45	38	38?	A.F.	4	65	0	Very fibrotic	—	++	+
A. A.	37	10	25	A.F.	*26*	—	—	Calcified, fragile	—	—	—
R. A.	31	11	22	*0.24*	15	45	0	Very fibrotic	—	—	(+)
A. L.	40	7	26	A.F.	12	210	20	Muscular	+	++	+
M. V. N.	37	17	33	0.20	7	125 *500*	0	Membranous	—	+	—

MATERIAL

As previously stated, our series of operated cases includes only patients with no demonstrable active rheumatic process. In all instances the operation did confirm the diagnosis of a mitral valvular lesion. It appears from Table I that only three patients had any noteworthy elevation of the sedimentation rate (B.O., E.R., and A.A.). In the first and the last cases this was probably due to the previous catheterization, and in the second one it was considered to be secondary to a severe acute cholecystitis some weeks earlier. In the latter case there were also a considerable elevation of the antistreptolysin titer and slight joint pains. The indications for operation were, however, urgent, as the patient had had two severe attacks of cholecystitis over a short period and the surgeon preferred to improve the patient's heart function before attempting an abdominal operation. It is remarkable that the antistreptolysin titer, as well as the sedimentation rate, decreased to normal values during the completely uneventful postoperative course. In the last case of the series, M.V.N., operation was performed despite an elevated antistreptolysin titer, as our previous experience seemed to make such a procedure permissible.

TABLE I (CONTINUED)*

			MYOCARDIUM		LUNG			
LYMPOCYTOSIS	ASCHOFF BODIES	BIOPSY DIAGNOSIS	LYMPOCYTES	ASCHOFF BODIES	STASIS	ARTERIOLAR THICKENING	FIBROSIS	PHAGOCYTES
(+)	(−)	−	Organized thrombosis	−	−			
(+)	(+)	+++	*Rheumatic endocarditis*	(+)	+			
(+)	+++	(+)	Lymphocytic endocarditis	++	(+)			
(+)	−	−	Organized thrombosis	++	−			
+	++	−	Lymphocytic endocarditis	−	−			
−	++	−	Organized thrombosis, lymphocytic endocarditis	++	−			
(+)	−	(+)	*Slight rheumatic endocarditis*	−	−			
(+)	(−)	++	*Rheumatic endocarditis*	−	−			
−	−	−	Organized thrombosis	−	−			
(+)	(−)	+++	*Rheumatic endocarditis*	−	−	−	+	−	++
+	−	(−)	Endocardial fibrosis	−	−	−	−	−	+
+	(+)	++	*Rheumatic endocarditis*	−	−	−	−	−	+
−	(+)	++	*Rheumatic endocarditis*	−	−	−	−	−	+
+	++	−	Organized thrombosis, lymphocytic endocarditis	++	−	−	++	−	(+)
−	−	−	Normal structure	−	−	−	−	++	++
(+)	(+)	++	*Rheumatic endocarditis*	+	−	−	−	(+)	+
+	+	−	Organized thrombosis	−	−	−	−	−	(+)
−	(+)	−	Organized thrombosis	−	−	−	−	+	+

*Symbols:
RHF = Rheumatic fever.
V.H.D. = Valvular heart disease.
P-Q = P-Q interval, sec.
ESR = Erythrocyte sedimentation rate, mm./hour.
ASL = Antistreptolysin titer.
ASE = Agglutination of sensitized erythrocytes.
A-VBII = Second degree atrioventricular block.
A.F. = Auricular fibrillation.
Pathologic figures are italicized.

METHODS

Specimens of the left auricular appendage were removed during operation, together with, in the latter part of the series (Cases 10 to 18), a part of the lingula lobe of the left lung for microscopic study.

Antistreptolysin titers were determined according to Kalbak-Ipsen[5] and the agglutination of sensitized erythrocytes according to Winblad.[6] Values of antistreptolysin titers exceeding 200 were considered abnormal. For agglutination of sensitized erythrocytes the corresponding figure was 20.

HISTOLOGIC ANALYSIS

From a pathologic-anatomic point of view the biopsies may be classified in four groups:

A. *Typical Subendocardial Rheumatic Endocarditis With Aschoff-Granuloma* (Figs. 1 and 2).—These cases were rich in subendocardially located, very typical

Aschoff granulomas with large histiocytic cells. In six cases (R.H., V.L., E.R., M.Ö., S.H., and R.A.) this picture was very marked. In another two (S.K. and E.B.) it was less pronounced; in patient S.K. there was also some lymphocytic endocarditis.

B. *Lymphocytic Endocarditis* (Fig. 3).—These cases had lymphocytic infiltrations, both in the endocardium, subendocardially, and in the myocardium. The findings probably represented an acute endocardial irritation. Four cases (E.A., S.K., M.N., and H.N.) belonged to this group.

Fig. 1.

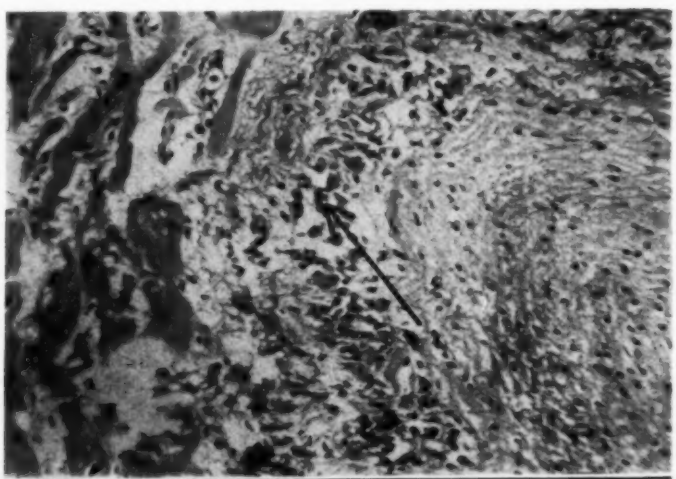

Fig. 2.

Fig. 1.—Subendocardial Aschoff granulomas in the patient R. A.
Fig. 2.—Subendocardial Aschoff granulomas in the patient R. H.

C. *Endocardial Thrombosis, and Organization of Such Thrombi, Including Endocardial Fibrous Thickening* (Fig. 4).—No less than eight cases (S.N., M.N., E.S., B.O., A.P., H.N., A.L., and M.V.N.) showed these features (in M.N. and H.N. together with lymphocytic endocarditis).

D. *No Pathologic Findings in Endocardium or Myocardium.*—In only one case (A.A.) were there no definite pathologic changes. Surprisingly enough, this was the largest heart in the material (total cardiac volume 2,150 c.c., determined according to Kahlstorf's formula).

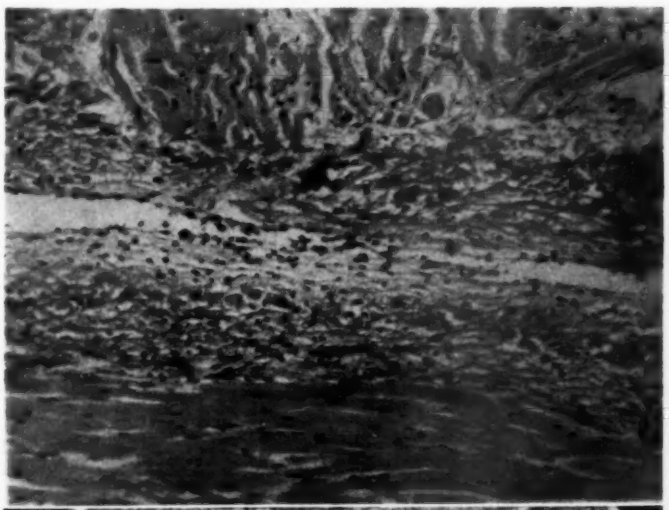

Fig. 3.

Fig. 4.

Fig. 3.—Lymphocytic endocarditis in the patient S. K.
Fig. 4.—Endocardial thickening from organization of thrombus in patient A. L. Arrows point to thrombi.

In patients with acute rheumatic endocarditis and Aschoff granulomas, the surface of the auricular endocardium appeared histologically smooth and displayed no old or recent thrombi. The lymphocytic endocarditis, on the contrary, had a tendency to thrombosis; one is sometimes in doubt whether these lymphocytic infiltrations are not mainly a part of a resorption process. However, lymphocytic endocarditis was also found without any signs of thrombosis and may, therefore, represent an acute endocarditic process.

Söderström,[7] in his analysis of the genesis of auricular thrombi, also frequently found endocardial lymphocytosis in organic heart disease. His observations that rheumatic granulomas are rare in cases with auricular thrombosis are also in agreement with our findings.

AUTOPSIES

Four patients in this series died, one in cardiac failure (B.O.*) fourteen months after the operation, the others (E.S., H.N., and A.A.) on the second to fourth day after operation. Autopsies have been performed on all of them.

PATIENT B. O.—The left auricle showed endocardial thickening due to organization of parietal thrombi, old and recent. There was no rheumatic or lymphocytic endocarditis, nor was there any sign of myocarditis. The mitral valve was thick, with beginning calcification at its base and moderate capillary infiltration. None of the other cardiac chambers showed any sign of endocarditis.

PATIENT E. S.—No Aschoff granulomas were found, neither in the endocardium nor in the myocardium of any of the cardiac chambers. There was no lymphocytic endocarditis. There was no other pathologic finding than the endocardial thickening due to an organized thrombosis, which already showed itself in the biopsy.

PATIENT H. N.—The left atrial endocardium showed a parietal thickening and a small lymphocytic infiltration between the endocardium and the myocardium. No other signs of lymphocytic or rheumatic endocarditis in any of the cardiac chambers.

PATIENT A. A.—In the left atrium, the parietal endocardium was generally somewhat thickened, but there was no rheumatic or lymphocytic endocarditis anywhere.

The autopsies in these cases were all completely in agreement with the biopsy picture. This obviously adds to the reliability of conclusions drawn from biopsy findings.

RESULTS

It appears from the table that out of eighteen cases operated upon for mitral stenosis and judged to be free from rheumatic activity (with the possible exception of the patient, E.R.), six showed definite signs of active rheumatic endocarditis and two minor signs. In three of these cases, rheumatic activity had probably persisted for at least twenty years. Except for the above-mentioned patient, E.R., the clinical examination and the laboratory tests did not point to any such activity. The highest antistreptolysin titers in the series were found in two patients with slight signs of rheumatic endocarditis and lymphocytic endocarditis and one patient with only organized thrombosis. In four cases of more severe rheumatic activity, the antistreptolysin titer was normal. The sedimentation rate appeared to be of no diagnostic value, and the same applied to prolongation of the P-Q interval. The agglutination of sensitized erythrocytes was normal in all our cases.

These results indicate that the usual laboratory tests of the type presented here cannot exclude the presence of active endocarditis in the left auricle. This,

*This was the only patient in the series where no radical operation could be performed because of a very small auricular appendage, which was obliterated at its base.

most likely, applies also to the mitral valve region. Definitely elevated antistreptolysin titers seem to be the most important signals, however.

From the observations presented in the table it would seem as if the rheumatic process might be of a long duration and still show marked signs of endocardial activity. With regard to the proper time for operation in patients with mitral stenosis we have hitherto taken into account the greater frequency of rheumatic "bouts" in childhood and youth and therefore thought it desirable to postpone operation until obvious manifestations of rheumatic activity were less likely to recur. There may, however, exist a continuous progress of rheumatic activity without recognizable acute exacerbations and if such is the case the above considerations would be less decisive.

We have, therefore, been interested to know whether persistent rheumatic activity of the endocardium goes with some particular type of valvular destruction, but we are not convinced that such is the case.

Organized thrombi were found in four of the six cases with auricular fibrillation and also in four of the twelve cases with regular rhythm. One patient in each group had a previous history of cerebral embolism; both died after operation. The immediate cause of death was in one case cerebral embolism; in the other there was no recent embolization and no major source of emboli within the auricle.

In the latter part of the series we also studied the pulmonary structure in a specimen from the lingula lobe, excised at operation. With regard to the limited number of observations, they will not be discussed here. These investigations continue, however, and will possibly be reported later.

CONCLUSIONS

The findings of active rheumatic lesions in resected left auricular appendages in cases without clinical and laboratory signs of active rheumatic carditis reported above must be considered of importance in the discussion of the surgical treatment of mitral stenosis. To our knowledge only one similar report[8] has been presented. On the whole, the same incidence of active rheumatic carditis (four cases of eleven) was found.

A survey of the methods used in the diagnosis of rheumatic fever[9] has recently been given. In this survey, the sedimentation rate is listed as number one among the laboratory aids available for the detection of active rheumatic fever. As shown above, this is not true with regard to the particular kind of rheumatic process manifested in these biopsies. Further studies are necessary to establish the best means to detect this particular phase of rheumatic activity. The clinical and prognostic significance of the findings, positive as well as negative, must also be investigated in future follow-ups.

Information as to the long-term fate of patients operated on for mitral stenosis is, for obvious reasons, limited. Scattered reports from early series indicate a favorable prognosis in the majority of cases.

It may be tempting to assume that persisting active rheumatic endocarditis is a serious menace to the long-term success of an operative procedure. It is possible, however, that the activity of the process is very low and that little harm will be done in the long run. Only experience can tell. So far, our second patient,

R.H., showed a +++ rheumatic endocarditis of the left auricular appendage. Our follow-up now covers sixteen months and her very marked clinical improvement after operation has not shown any rebound. In the shorter observation period of six months, the second +++ endocarditis patient, E.R., has, likewise, showed continuous improvement.

For the practical management of these patients, the conclusion may be drawn that rheumatic endocarditis can be present in spite of negative clinical findings and negative laboratory tests. Although we do as yet lack any proof that persisting rheumatic endocarditis of the type described is a menace to the success of the operation, we hesitate to draw definite conclusions from our present limited material. If persisting rheumatic activity still is to be regarded as an unfavorable condition, it may nevertheless be maintained that *one* positive test is not enough to advise against operation, but if *two* of the tests are positive, the case should be carefully reconsidered before action is taken. Only later follow-ups will disclose whether also this caution is unnecessary.

SUMMARY

The possibilities of clinical and laboratory diagnosis of active rheumatic processes in the heart of each patient to be operated upon for mitral stenosis are discussed on the basis of biopsies from left auricular appendages, resected at operations for mitral stenosis. Rheumatic activity was found to be present in spite of negative clinical and laboratory findings. Pathologic sedimentation rate or antistreptolysin titers alone should not be regarded as positive evidence of such activity. Long-term follow-ups are necessary to evaluate the importance of active rheumatic endocarditis for the prognosis in operated cases of mitral stenosis.

REFERENCES

1. Glover, R. P., Bailey, C. P., and O'Neill, T. S. E.: Surgery of Stenotic Valvular Disease of the Heart, J. A. M. A. **144**:1049-1057, 1950.
2. Baker, C., Brock, R. C., and Campbell, M.: Valvulotomy for Mitral Stenosis, Brit. M. J. **1**:1283, 1950.
3. Bland, E. F.: Surgery for Mitral Stenosis, Circulation **5**:290-299, 1952.
4. Wulff, H. B., Biörck, G., Bergh, N. P., Krook, H., Axén, O., and Lundskog, O.: Studies on Mitral Stenosis. I. Results of One Year's Series of Surgically Treated Cases. In print.
5. Ipsen, J.: A Standard for Antistreptolysin O of Human Serum, and Its Practical Application, Acta path. et microbiol. Scandinav. **21**:203-213, 1944.
6. Winblad, S.: Hemagglutination as a Diagnostic Method With Special Reference to the Application of the Method Using Sensitized Sheep Cells, Acta path. et microbiol. Scandinav. Suppl. **91**:115-125, 1951.
7. Söderström, N.: Myocardial Infarction and Mural Thrombosis in the Action of the Heart, A Thesis, Acta med. Scandinav. Suppl. 217, 1948.
8. Kuschner, M., Ferrer, I., Harvey, R. M., and Wylie, R. H.: Rheumatic Carditis in Surgically Removed Auricular Appendages, Am. Heart J. **43**:286-292, 1952.
9. Griffith, G. C., and Scheinkopf, J. A.: Diagnosis and Differential Diagnosis of Rheumatic Fever, Acta med. Scandinav. **142**:429-438, 1952.

RHEUMATIC HEART DISEASE WITH CALCIFICATION OF THE LEFT AURICLE

Report of Two Cases With Review of the Literature

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CALCIFICATION in the left auricular (atrial) wall is rare and in the majority of recorded instances it has been associated with rheumatic heart disease involving the mitral valve. Although for many years autopsy reports have mentioned the finding of such calcification in cases of long-standing rheumatic disease, its radiologic recognition is far more recent, the first case being recorded by Shanks, Kerley, and Twining in 1938.[13]

Since then Begg[2] has described one case, and Epstein[4] collected three examples of this condition. Schwedel's[12] illustration of a patient with left auricular calcification is one of the three reported by Epstein. Two series of cases of this condition have recently been published. Miller and associates[10] described eight cases and Young and Schwedel[15] presented four additional ones. Fainsinger[6] reported one case, making a total of eighteen examples of left auricular calcification associated with rheumatic valvular disease diagnosed during life.

It is the purpose of this communication to present two further cases of massive calcification occurring in the left auricle in rheumatic heart disease, to review the cases already published, and to discuss some of the clinical features met with in this condition.

Pathology.—The changes in the left auricle described originally by MacCallum[9] and elaborated later by Von Glahn[14] and Gross[7] are generally accepted as those produced by rheumatic disease. Briefly, these changes consist of subendocardial plaques, endocardial fibrosis, connective tissue hyperplasia, and Aschoff nodules. The site of the predilection for endocarditis is the posterior wall of the auricle above the posterior mitral leaflet. Koletsky[8] found involvement of the endocardium of the left auricle in sixty of one hundred rheumatic hearts. All sixty cases had mitral valvulitis, fifty-seven had aortic valvulitis, and forty-two had involvement of the tricuspid valve. The incidence of auricular lesions was related to the severity of the valvular disease, especially mitral; similarly those hearts which showed gross left auricular endocarditis were usually widely involved by the rheumatic process.

The occurrence of endocardial calcification in pathologic studies of rheumatic hearts has been noted repeatedly but it is a relatively infrequent finding. When calcification is extensive and involves most of the left auricular wall, it is reasonable to assume that the heart has been the site of severe carditis.

Six cases of left auricular calcification diagnosed during life have been examined post mortem. In each case the left auricular calcification was endo-

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cardial, the extent varying from plaques in the posterior wall to involvement of the entire wall. Other endocardial changes included thickening, hyalinization, and fibrosis. In four there was a partially adherent thrombus in the left auricle which was itself not calcified. In all cases there was mitral stenosis with a varying degree of incompetence. In four cases the aortic valve exhibited either stenosis, or incompetence, or both. The tricuspid valve was involved in a similar manner in five cases. All three valves were affected in three cases. The annulus of the mitral valve was calcified in one case and the mitral valve cusps in three. There was aortic cusp calcification in two cases. The only extracardiac calcification noted was a staghorn calculus of the left kidney in one case and calcification in the medullary region of the left kidney in another.

CASE REPORTS

CASE 1.—J. W., a 53-year-old widow, was admitted to the Johannesburg General Hospital in May, 1949, complaining of breathlessness on exertion with swelling of the legs and abdomen of two weeks' duration. Twenty-one years previously she had experienced a prolonged febrile illness for which she had been hospitalized and which was diagnosed as rheumatic fever with carditis. She required seven months in which to convalesce after which she remained well for approximately eight years. In 1936 the patient experienced sudden weakness of the left arm and leg which was thought to be due to a cerebral embolus. From then on, she had repeated attacks of breathlessness, cough, swelling of the legs, and an irregular pulse for which she was treated by many doctors with digitalis and mercurial injections. Two weeks prior to admission her symptoms returned and she was now unable to walk at all without choking nor could she lie flat. She also complained of a productive cough and nausea.

Examination revealed an orthopneic adult woman with a mitral facies and cyanosis of ears, nose, cheeks, and extremities. Respiration was labored and the rate was 34 per minute. The cardiac rate at the apex was 90 per minute and the rhythm completely irregular. There was venous pulsation 7 cm. above the manubrium. The heart was grossly enlarged to the left, the impulse being diffuse and forceful, and apical systolic and diastolic thrills could be felt. There was a loud, harsh systolic murmur and a mid-diastolic rumble in the mitral area. The pulmonary second sound was greatly accentuated. The blood pressure was 130/90 mm. Hg. An impaired percussion note was found at both lung bases with diminished air entry and crepitations. The liver was grossly enlarged, smooth, tender, and pulsated. There was edema of both legs. The left arm and leg showed some diminution of motor power but there was no spasticity or increase in reflexes and the plantar responses were flexor on both sides. Albuminuria was present.

The electrocardiogram showed auricular fibrillation with evidence of right ventricular hypertrophy. X-ray examination revealed gross cardiac enlargement involving the right ventricle and the left auricle, the latter chamber showing massive calcification in its wall. There was also enlargement of the pulmonary arteries and both pulmonary bases showed congestive changes. Mitral stenosis and incompetence, relative tricuspid incompetence, auricular fibrillation with congestive cardiac failure, and calcification of the left auricle due to rheumatic carditis were diagnosed.

Treatment consisted of a low-sodium diet, digitalis, frequent injections of mercurial diuretics, and ammonium choloride. Within two weeks all evidence of congestive cardiac failure disappeared and the patient was able to leave hospital on maintenance therapy.

However, her improvement was not maintained and she was readmitted in October of the same year, her condition being similar to that described above. In addition there was evidence of a right-sided pleural effusion and ascites. The same treatment was again undertaken but

from this time onward all measures directed at the cardiac failure were only partly successful. Methyl thiouracil in doses of 200 mg. at eight-hour intervals was given in an attempt to diminish her oxygen requirements but it did not have any obvious effect after a trial lasting several months. During this admission evidence of liver and renal damage was obtained. After four months, the patient was discharged slightly improved. She continued to be treated at home during the next year, but she was almost completely incapacitated. She died early in 1951 at the age of 54. Permission for post-mortem examination could not be obtained.

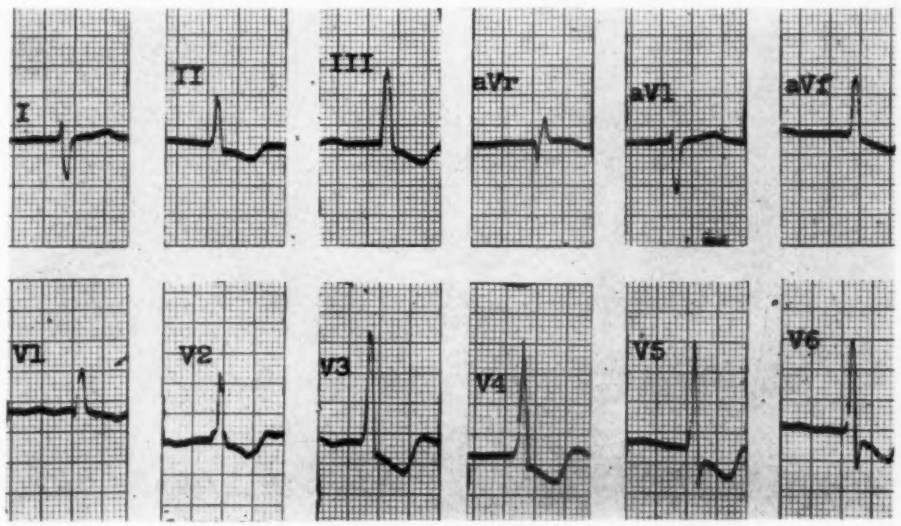

Fig. 1 (Case 1).—Electrocardiogram of Case 1 taken on Dec. 22, 1949.

Fig. 2 (Case 1).—Teleradiogram of Case 1 showing a grossly enlarged heart, prominent pulmonary conus, and congestive changes in both lung fields. The cardiac outline shows the configuration of mitral valve disease.

After the diagnosis of calcification of the left auricle was made in 1949 the electrocardiogram remained constant except for the degree of digitalis effect on the S-T segments (Fig. 1). The radiologic appearances did not change and the plates shown in Figs. 2 to 4 are typical of the findings.

CASE 2.—H. P., a 44-year-old woman doctor was first seen in January, 1949. At the age of 8 years she had suffered from pains in her joints, and rheumatic infection was suspected. At the age of 19, while she was a medical student, mitral stenosis was diagnosed but she remained symptom free till she was 27 when her effort tolerance began to decrease. Two years later in 1936 her legs began to swell and in 1938 she had her first paroxysm of auricular fibrillation

Fig. 3.

Fig. 4.

Fig. 3 (Case 1).—Right anterior oblique teleradiogram with a barium swallow showing the curvilinear left auricular calcification lying in the posterior part of the cardiac shadow and showing the classical relationship to the barium-filled esophagus.

Fig. 4 (Case 1).—A penetrated teleradiogram showing the extensive curvilinear calcification lying in the left auricle.

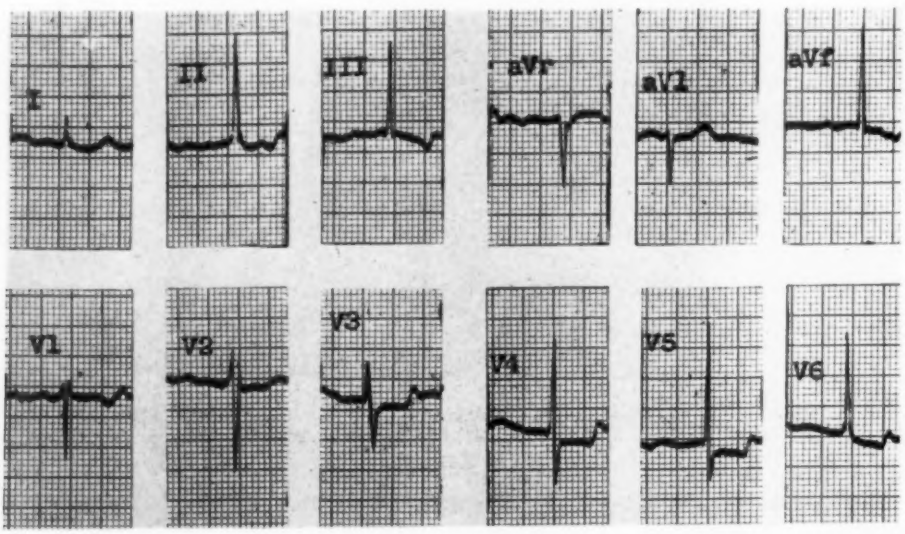

Fig. 5 (Case 2).—Electrocardiogram of Case 2 taken on Dec. 20, 1950.

which arrhythmia became established the following year. At about this time she began to have attacks of bronchitis each winter but some of these attacks were associated with what was called congestion of the lungs. They were characterized by fever, rusty sputum, and evidence of consolidation, usually of the left lung. The winter months became a serious problem because of these recurrent pulmonary episodes.

Frank congestive cardiac failure occurred on a number of occasions leading to hospitalization in 1943, 1945, and 1947. Although she improved rapidly when treated with bed rest, digitalis, and mercurials, some degree of failure persisted. In spite of these difficulties she was able to work in the casualty department of a hospital except for short periods when she was forced to rest in bed.

Examination in 1949 showed a well-nourished adult woman with a malar flush and cyanosis of the lips and ears. She was orthopneic, but the venous pressure was not raised. The pulse rate was 80 per minute and the rhythm grossly irregular. The blood pressure was 120/80 mm. Hg. The heart was greatly enlarged and there was a mitral mid-diastolic rumbling murmur preceded by an accentuated first sound. The pulmonary second sound was very loud. There were crepitations at both bases and the liver was considerably enlarged. Edema of the legs was also present.

The electrocardiogram showed evidence of right ventricular hypertrophy and auricular fibrillation (Fig. 5). An x-ray study in 1948 showed gross cardiac enlargement with extensive left auricular calcification. The lung fields presented changes suggestive of hemosiderosis (Figs. 6 to 8).

She was treated by means of a low-sodium diet, digitalis, and mercurial diuretics and was able to continue at her work until early in 1951 when she was forced to terminate her medical career because of failing health. Re-examination in June, 1951, showed the same clinical findings described above except that the liver edge could just be felt and there was no edema of the legs. The patient was recovering from another chest episode and looked ill, having lost weight. She refused to keep to a low-sodium diet but her failure was reasonably well controlled by digitalis and 2 c.c. of a mercurial diuretic given intramuscularly on alternate days.

CLINICAL FEATURES

A summary of the eighteen cases of left auricular calcification collected from the literature and the two reported above is contained in Table I. Adequate clinical data were available in nineteen cases, of which fourteen were women and five were men. Their ages ranged from 34 to 73 years, the average being 51 years. Ten patients died of their cardiac disease, the average age at death being 53 years. In seventeen cases the average length of history of rheumatic infection was twenty-nine years and in eighteen cases the average length of symptoms was seventeen years. The first manifestations of rheumatic disease occurred after the age of 20 in eight cases, six of which have already died.

Clinically the mitral valve was involved in all twenty cases, nineteen of which had definite stenosis; the aortic valve was also affected in eight. Tricuspid disease was diagnosed correctly during life in three and found at autopsy in two cases.

Auricular fibrillation was present in eighteen cases, the average duration in thirteen being ten years. In one case it had been present for twenty years. In eight fatal cases the average duration was eight and one-half years. Congestive cardiac failure was found in sixteen cases with an average duration of eleven years. Excluding one patient who died of the effects of carcinoma of the large bowel, the average duration of congestive failure in nine fatal cases was ten years. Hypertension was present in three cases and evidence of coronary artery disease in one.

TABLE I. SUMMARY OF FINDINGS IN TWENTY CASES OF LEFT AURICULAR CALCIFICATION DIAGNOSED DURING LIFE

AUTHOR	SEX	AGE (YEARS)	LENGTH OF RHEUMATIC HISTORY (YEARS)	DURATION OF SYMPTOMS (YEARS)	VALVES AFFECTED CLINICALLY	ARRYTHMIA—DURATION (YEARS)	CONGESTIVE CARDIAC FAILURE—DURATION (YEARS)	CALCIFICATION OF OTHER STRUCTURES (RADIOLOGIC)	POST-MORTEM FINDINGS	MISCELLANEOUS
Kerley et al.[13]					Mitral					
Begg[2]	F	61	30	7	Mitral Aortic	AF		M & A valves RA	Died—no autopsy	Hypertension
Epstein[4]										
Case 1	F	45	20	20	Mitral	AF—10	Absent	M valve		
Case 2	F	35	26	12	Mitral	AF—12	12			
Case 3	F	49	29	20	Mitral	AF—20	20	M valve		
Miller et al.[10]										
Case 1	M	51	20	20	Mitral, Aortic Tricuspid	AF—3	5		MS MI TS TI AI Thrombus in LA	
Case 2	M	73	—	2	Mitral	AF—2	2		MS MI A & M valves calcified	Died of carcinoma of bowel
Case 3	F	56	30	19	Mitral	AF—2	6		MI MS M valve calcified T valvulitis Thrombus in LA	
Case 4	M	49	14	14	Mitral, Aortic Tricuspid	AF—14	14		MS AS M & A valves calcified Coronary sclerosis	Coronary artery disease

Case 5	F	52	43	22	Mitral	AF & Flutter 10	17		MS & TS	
Case 6	M	66	26	14	Mitral Aortic	AF—6	8		Died—no autopsy	
Case 7	F	51	39	34	Mitral	AF	15			
Case 8	F	59	54	25	Mitral Aortic	AF	1			
Young and Schwedel[12] Case 1	M	37	24	6	Mitral, Aortic Tricuspid	AF	6		MS MI TS TI AS AI M valve calcified	
Case 2	F	48	15	15	Mitral Aortic	AF	14			Hypertension
Case 3	F	52	40	27	Mitral Aortic	AF—17	18		Died—no autopsy	
Case 4	F	48		10	Mitral	AF—3	3		Died—no autopsy	Hypertension
Fainsinger[6]	F	34	27	5	Mitral	Sinus rhythm	Absent			
Present Authors Case 1	F	54	22	22	Mitral	AF—14	14		Died—no autopsy	
Case 2	F	44	36	17	Mitral	AF—13	15			

Key: M = Mitral. A = Aortic.
MS = Mitral stenosis. MI = Mitral incompetence. TS = Tricuspid stenosis. TI = Tricuspid incompetence.
AS = Aortic stenosis. AI = Aortic incompetence. AF = Auricular fibrillation. LA = Left auricle. RA = Right auricle.

Fig. 6.

Fig. 7.

Fig. 8.

Fig. 6 (Case 2).—Teleradiogram of Case 2 showing a greatly enlarged heart with the classical configuration of mitral valvular disease. A moderate degree of engorgement of the pulmonary circulation is present and a fine reticulation suggestive of hemosiderosis was visible throughout the lung fields.

Fig. 7 (Case 2).—A hard penetrated film of the heart showing the enlarged and almost completely calcified left auricle.

Fig. 8 (Case 2).—A right anterior oblique teleradiogram with a barium swallow showing the enlarged calcified left auricle indenting and bulging into the esophagus.

RADIOLOGIC FEATURES

The radiologic appearances of left auricular calcification are now well established. The calcification is generally curvilinear in character and occupies a position posterior to the base of the heart. As it is associated with mitral valve disease, some enlargement of the left auricle is usually present and consequently the arc of calcification is larger than one would anticipate. Such calcification may not be seen in the posteroanterior view and is usually more obvious in the right anterior oblique position where its relation to the displaced, barium-filled esophagus can be clearly demonstrated. In the left anterior oblique position the calcified auricle may or may not displace the left main bronchus in an upward direction. Calcification in the auricular wall may escape detection if over-penetrated films are not taken.

Calcification in other cardiac structures, such as pericardium (Figs. 9 and 10), ventricular myocardium, coronary arteries, annulus fibrosis, and valves, are not likely to be confused with left auricular calcification. Very occasionally a mural thrombus in the left auricle becomes calcified but massive thrombi do not calcify (Evans and Benson[5]). There was no calcification within the thrombi found in four of the cases described above which came to autopsy.

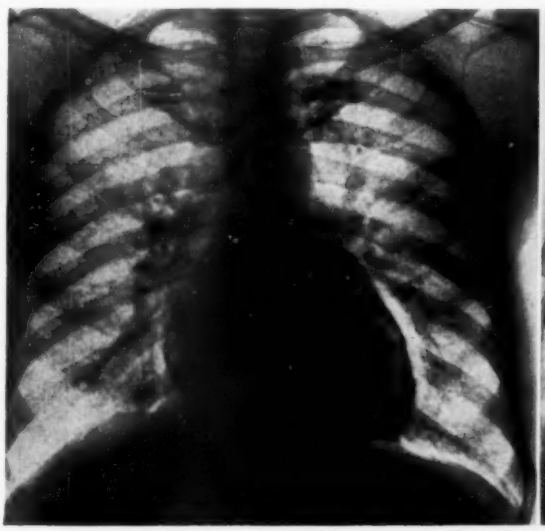

Fig. 9.

Fig. 10.

Fig. 9.—Teleradiogram showing pericardial calcification. Pericardiac calcification is usually far more extensive than calcification in the left auricle and bears only a superficial resemblance to the latter condition.

Fig. 10.—Left anterior oblique view of the same case as shown in Fig. 9, demonstrating the extensively calcified pericardium.

DISCUSSION

Calcification of the left auricular wall is known to occur in certain conditions, for example, metastatic calcification associated with bone disease, chronic renal disease, hyperparathyroidism, and that due to hypervitaminosis D (Mulligan[11]), but it is generally not sufficiently massive to be recognized during life. The

combination of radiologically demonstrable calcification with evidence of mitral valvular disease indicates with reasonable certainty the rheumatic nature of the process.

Young and Schwedel[15] state that patients with left auricular calcification do not differ clinically from other cases of advanced rheumatic heart disease with predominant mitral stenosis. However, a study of some of the features of these cases suggests that certain differences do exist.

Although the number of cases of mitral valve disease with calcification of the left auricle is small, the clinical course of the majority has been strikingly similar. This course is unusual when one takes into account the severe degree of rheumatic infection implied by the presence of massive auricular calcification. Patients with left auricular calcification are adults with long-standing rheumatic disease who continue to live for many years after the onset of symptoms.

TABLE II. COMPARATIVE COURSE OF CASES OF RHEUMATIC HEART DISEASE WITH AURICULAR CALCIFICATION AND CASES OF MITRAL STENOSIS OVER THE AGE OF 50 YEARS

	AURICULAR CALCIFICATION (19 CASES)	MITRAL STENOSIS PATIENTS OVER AGE OF 50 (COOKSON[3]) (38 CASES)
Length of rheumatic history (years)	14 to 54 Average 29	20 to 50
Average duration of symptoms (years)	17 Range 5 to 34	4.5 Range 1 to 25
Incidence of auricular fibrillation (per cent)	90	92
Average duration of auricular fibrillation (years)	10 Range 2 to 20	4.5
Incidence of congestive cardiac failure (per cent)	80	67
Average duration of congestive cardiac failure (years)	11 Range 1 to 20	4.5
Incidence of hypertension	16 % ±8.19	50 % ±8.19
Number of fatal cases	10	16
Average age at death (years)	53 Range 37 to 66	62

Among the factors which influence the course of rheumatic heart disease at any age are the onset of auricular fibrillation and/or congestive cardiac failure. These events have serious prognostic significance in adults with rheumatic heart disease. Nevertheless, patients with auricular calcification, most of whom appear to develop both complications, are able to live for long periods in spite of them.

There are also differences between patients with auricular calcification and those over the age of 50 with mitral stenosis (Table II). Appel and Kossman[1] studied seventy-one patients with rheumatic heart disease over the age of 60

years and, of all the possible factors in longevity which could be analyzed, only the late age of onset of rheumatic infection appeared to have statistical significance in determining long life with rheumatic heart disease. The number of patients with auricular calcification was too small to be evaluated with regard to this factor but since approximately one-half the patients with auricular calcification contracted rheumatic infection before the age of 20 and six of the eight patients who contracted it after the age of 20 have already died, the late onset of such infection does not appear to be responsible for the better prognosis.

It is conceivable that calcification of the left auricle might have a deleterious effect on the course of rheumatic mitral valve disease. Yet patients with such calcification appear to fare somewhat better than the average adult with mitral stenosis. It is possible that calcium is deposited gradually in the auricular wall and a period of many years is required before it becomes massive enough to be radiologically demonstrable.

SUMMARY

1. The literature with regard to cases of rheumatic heart disease with left auricular calcification diagnosed during life has been reviewed.

2. Two additional cases were described.

3. Massive left auricular calcification should be looked for in cases of rheumatic heart disease with a long history of auricular fibrillation and congestive cardiac failure.

REFERENCES

1. Appel, S. B., and Kossmann, C. E.: J. A. M. A. **146**:1474, 1951.
2. Begg, A. C.: New Zealand M. J. **44**:315, 1945.
3. Cookson, H.: Brit. Heart J. **11**:155, 1949.
4. Epstein, B. S.: Am. J. Roentgenol. **61**:202, 1949.
5. Evans, W., and Benson, R.: Brit. Heart J. **10**:39, 1948.
6. Fainsinger, M. H.: South African M. J. **25**:233, 1951.
7. Gross, L.: Am. J. Path. **11**:711, 1935.
8. Koletsky, S.: Am. Heart J. **29**:739, 1945.
9. MacCallum, W. G.: Bull. Johns Hopkins Hosp. **35**:329, 1924.
10. Miller, G., Becker, I. M., and Taylor, H. K.: Am. Heart J. **40**:293, 1950.
11. Mulligan, R. M.: Arch. Path. **43**:177, 1947.
12. Schwedel, J. B.: Clinical Roentgenology of the Heart, New York, 1946, Paul B. Hoeber, Inc., p. 367.
13. Shanks, S. C., Kerley, P., and Twining, E. W.: A Text Book of X-ray Diagnosis, Vol. 1, London, 1938, H. K. Lewis & Co., Ltd., p. 50.
14. Von Glahn, W. C.: Am. J. Path. **2**:1, 1926.
15. Young, D., and Schwedel, J. B.: Am. Heart J. **40**:771, 1950.

CONGENITAL PULMONIC STENOSIS WITH OPEN FORAMEN OVALE IN INFANCY

Report of Five Proved Cases

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PULMONIC stenosis with an open foramen ovale, though less frequently found than the tetralogy of Fallot, may prove to be a common cause of a cyanotic congenital cardiac malformation. Abbott's[2] study of 1,000 cases of congenital heart disease showed only sixteen instances of pulmonic stenosis with patent foramen ovale. That this lesion is not rare has only recently been suspected.[1] At this hospital we have had five infants with this malformation. With continuing study the clinical picture is becoming clarified. Selzer and associates,[3] Allanby and Campbell,[4] and Engle and Taussig[5] have established the syndrome. The first-named authors reviewed the literature and described twenty-nine cases proved by autopsy, including two of their own. Allanby and Campbell described five cases, four proved by post-mortem examination.

Engle and Taussig reported three cases proved at autopsy. The correct diagnosis is important because the indicated operation of pulmonic valvulotomy may be lifesaving. The Potts-Smith and the Blalock-Taussig operations should be avoided as either may result in heart failure.

Terminology.—The use of several different titles to designate this single condition has resulted in confusion. Examples include: syndrome of pulmonary stenosis with patent foramen ovale,[3] valvular pulmonic stenosis with intact ventricular septum and patent foramen ovale,[5] congenital pulmonary stenosis with closed ventricular septum,[4] congenital pulmonary stenosis with intact ventricular septum,[6] trilogy of Fallot,[8] pulmonary stenosis without ventricular septal defect, pulmonary stenosis with reversed interatrial shunt,[42] congenital stenosis of the pulmonic valve with associated auricular septal defect,[43] and pure or simple or isolated[16] pulmonary stenosis. For a malformation which is common, it does not seem appropriate to include as part of its name the simple fact that the ventricular septum is intact—a normal finding has no purpose in its title. Furthermore, as stated by Wood,[9] who also objects to this phrase, a small ventricular septal defect may not interfere with its clinical features. The usually stated purpose for including the phrase, "intact ventricular septum," is to clearly differentiate the condition from the tetralogy of Fallot (pulmonary stenosis, ventricular septal defect with overriding aorta, and right ventricular hypertrophy).

Pathology.—The pathologic findings of the condition are: First, a stenosis of the pulmonic valve.[10] This is usually a special type of stenosis. The three

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cusps are fused into a single dome-shaped diaphragm, projecting into the pulmonary artery, with a tiny central perforation ranging from about 0.5 to 4 mm. in diameter. Second, the foramen ovale is open. In the earlier stages of this malformation, the foramen may be functionally closed. Third, the pulmonary artery distal to the stenosis is thin-walled and dilated. Fourth, the right side of the heart is hypertrophied and often dilated. It seems that the best term to designate this condition is pulmonic stenosis with open foramen ovale.

PATHOLOGIC PHYSIOLOGY

The stenotic valve interferes with the passage of the blood from the right ventricle into the pulmonary artery. The right ventricle hypertrophies in response to increased work. Pressure in the right ventricle as determined by cardiac catheterization is very high. The systolic pressure is usually over 100 mm. Hg and occasionally exceeds 200 mm. Hg (normal 25). Eventually, the right atrium dilates and gradually the unsealed foramen ovale is spread open. The patency of the foramen ovale is therefore not a true congenital malformation; it results from the dilatation of the right atrium. In 25 per cent of routine autopsies on adults, probe patency of this foramen is found.[11] When pulmonic stenosis is present, there is probably less tendency for the foramen to close.[12] The pressure in the right atrium becomes elevated and eventually exceeds that in the left atrium and there results a right-to-left shunt through the open foramen ovale. When this equals about 30 per cent of the right atrial intake, cyanosis occurs. Wood[9] has described an instance of mild pulmonic stenosis with open foramen ovale in which the shunt was left-to-right; obviously, in this case, there would be no cyanosis. Engle and Taussig[5] catheterized a pulmonary vein in one case and found it to be 97 per cent saturated with oxygen in a cyanotic patient. A characteristic feature of this malformation is dilatation of the pulmonary artery, but the mechanism of the poststenotic dilatation is unknown.[4,13]

CASE REPORTS

CASE 1 (2354001).—A 3-month-old white girl had showed slight cyanosis at birth and a loud precordial systolic murmur had been present. The cyanosis regressed after the tenth day, and one month later her color was normal. When 2 months old, she developed a severe respiratory tract infection and there was a reappearance of slight cyanosis followed by the development of apneic periods requiring artificial respiration. She had generalized convulsive seizures with a temperature of 104° F. (rectal); she was then brought to the hospital. She was very ill with irregular respirations of 40 per minute of Cheyne-Stokes type, with long periods of apnea. She seemed almost lifeless, giving no sign of recognition to external stimuli. The chest was clear and without deformity. The systolic murmur was maximal in the left third intercostal space and was loud, but no thrill was felt. The heart was enlarged (Fig. 1). The liver was palpable 3 fingerbreadths below the right costal margin but pulsations were not felt. No clubbing of the fingers or the toes was found. An electrocardiogram (Fig. 2) showed prominent P waves and right ventricular hypertrophy.

After treatment with penicillin and oxygen, she became afebrile and showed steady improvement in color and respirations, but the cyanosis was still noticeable in the lips, palms, and soles. One week after admission to the hospital, she had a sudden episode of dyspnea and increase in cyanosis. These continued to recur, with respirations reaching 80 per minute and heart rate 150 per minute, and she died after five days.

The anatomic diagnosis* was: valvular pulmonic stenosis, dilated pulmonary artery, patent foramen ovale, patent ductus arteriosus, right ventricular hypertrophy, a solitary fibrous and partially calcified pedunculated node in the pulmonary artery at the site of the ostium of the

Fig. 1 (Case 1).—A chest roentgenogram of the patient at the age of 3 months. The heart is enlarged, and the cardiothoracic ratio is 8.2/12.2 or 67 per cent. The pulmonary artery salient is full and the vascular markings in the lung fields are diminished.

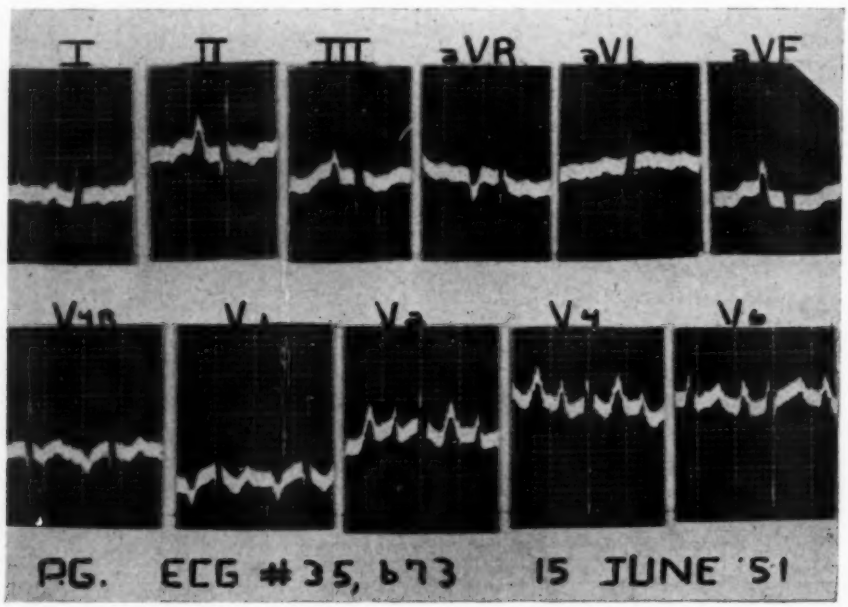

Fig. 2 (Case 1).—An electrocardiogram taken at the age of 3 months. The rate is 145 per minute with sinus rhythm. The P-R interval is 0.15 second, the QRS width 0.07 second, and there is right axis deviation of plus 130 degrees. There are tall peaked P waves in Leads II and aV_F, low amplitude and diphasic T waves in Lead I, and tall R waves in Leads V_{4R} and V_1 followed by diphasic T waves. The intrinsic deflection over the right precordium is 0.03 second. There are deep S waves in Leads V_2, V_4, and V_6, followed by upright T waves. These findings are diagnostic of right ventricular hypertrophy and first-degree atrioventricular block. Atrial hypertrophy is suggested.

*Post-mortem examination by Major Harry F. Sproat, Medical Corps, United States Army.

ductus arteriosus, and atelectasis of the lungs. The small vegetation on the anterior wall of the pulmonary artery was so situated that it partially occluded the lumen of the ductus. The foramen ovale was patent, measuring 1.0 by 0.5 cm. in diameter. The ventricular septum was intact. The pulmonic valve was markedly stenotic, consisting of a circular dome-shaped valve with a tiny central perforation.

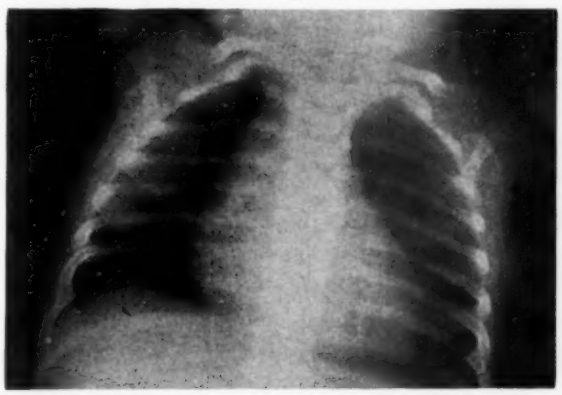

Fig. 3 (Case 2).—A chest roentgenogram taken at the age of 3 months. The heart is slightly enlarged with a cardiothoracic ratio of 6.9/12.3 or 56 per cent. The pulmonary artery salient appears normal and the vascular markings are decreased.

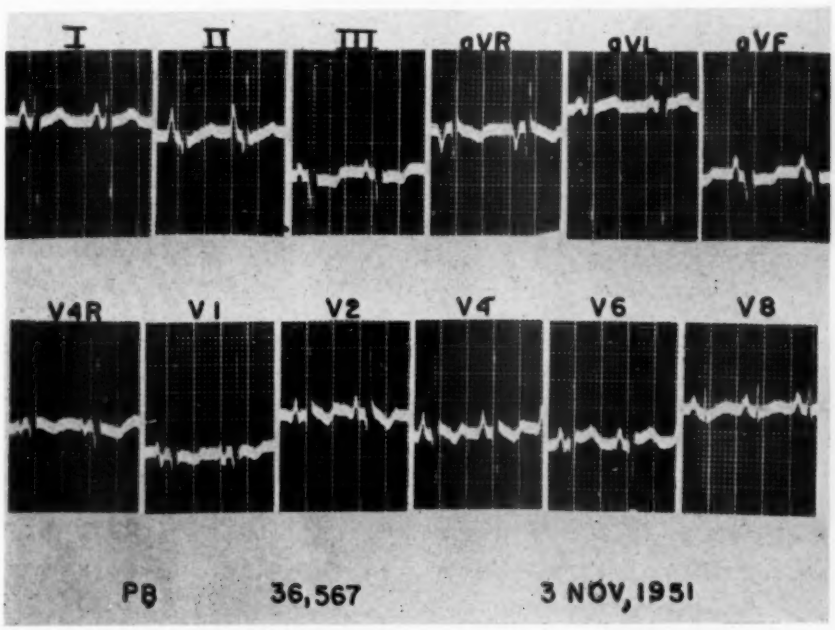

Fig. 4 (Case 2).—An electrocardiogram taken at the age of 4 months. The rate is 120 per minute with sinus arrhythmia. The P-R interval measures 0.10 second, the QRS width 0.06 second. There is right axis deviation of plus 117 degrees. The P waves are tall and peaked in Leads I, II, aV_F, V_2, and V_4, and are prominent and diphasic in Lead V_1. There are deep S waves in Leads I and aV_L and tall R waves in Lead III. T waves are diphasic in Leads III and aV_F. There are tall R waves followed by inverted T waves in Leads V_{4R}, V_1 and V_2. The S waves are prominent in Leads V_4 and V_6, and the T waves are diphasic in V_4 and upright in Leads V_6 and V_8. These findings denote right atrial and right ventricular hypertrophy.

CASE 2 (2491030).—A 4-month-old white girl was cyanotic at birth and had a precordial systolic murmur. When first examined at our clinic, she was 3 months old and showed a moderate degree of generalized cyanosis. A moderate (Grade III) systolic murmur was heard with maxi-

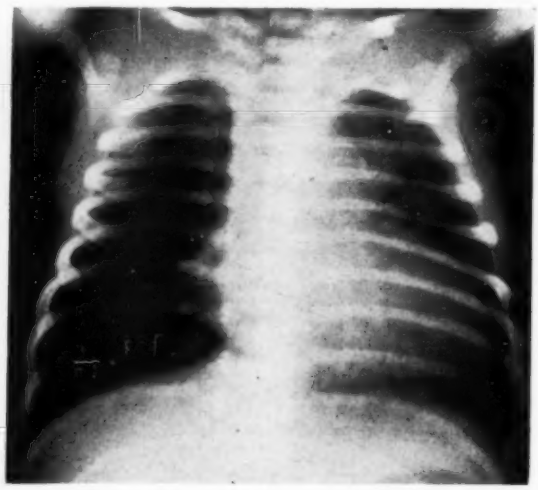

Fig. 5 (Case 3).—A chest roentgenogram taken on the day of birth shows an enlarged heart with the cardiothoracic ratio of 6.0/9.7 or 62 per cent. The apex is lifted up, the pulmonary artery segment is not full, and the pulmonary vascular markings are diminished.

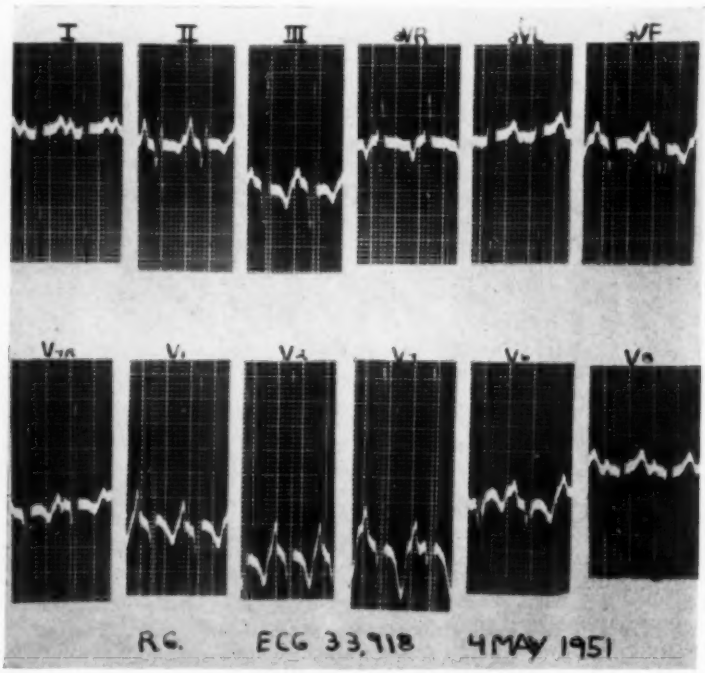

Fig. 6 (Case 3).—An electrocardiogram taken at the age of 7 months. Sinus tachycardia of 160 per minute is present. The P-R interval is 0.11 second, the QRS width 0.08 second, and there is right axis deviation of plus 138 degrees. There are tall peaked P waves in Lead II, deeply notched R waves in Lead II, inverted T waves in Leads II, III, and aV_F, flat T waves in Lead aV_R, tall R in Leads V_{4R}, V_1 to V_6, followed by an inverted T wave and deep S waves in Lead V_8 accompanied by upright T waves. These findings are diagnostic of sinus tachycardia, right ventricular hypertrophy, and atrial hypertrophy.

mum intensity in the left third and fourth intercostal spaces and this was accompanied by a slight thrill in the same area. The heart was slightly enlarged (Fig. 3). The liver and spleen were not palpable. An electrocardiogram (Fig. 4) showed prominent P waves and right ventricular hypertrophy.

At the age of 4 months, she had an attack of apnea requiring artificial respiration during a low-grade respiratory tract infection. She continued to have repeated attacks of paroxysmal dyspnea which could be relieved by placing her in the knee-chest position and administering morphine. The cyanosis became progressively more marked. She was transferred by air to another hospital but died before operation could be performed.

The anatomic diagnosis* was: valvular pulmonic stenosis, patent foramen ovale, right ventricular hypertrophy, tricuspid stenosis (mild), and endocardial fibroelastosis (mild, right ventricle). The heart was enlarged, weighing 58 grams (normal 23 grams). The pulmonic valve was markedly stenotic, consisting of three thickened cusps and measuring 0.2 cm. in circumference. The pulmonary artery was small as were its branches. The other valves were normal except that the tricuspid valve was slightly stenotic and measured 5.5 cm. in circumference. The foramen ovale was patent anatomically and functionally. The ventricular septum was intact. The ductus arteriosus was closed. There was congestion of the gastrointestinal tract, liver, kidneys, and brain, and congestion and atelectasis of both lungs.

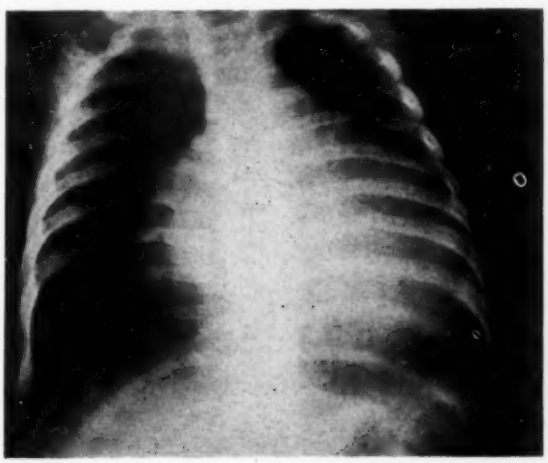

Fig. 7.

Fig. 8.

Fig. 7 (Case 3).—A chest roentgenogram taken at 8 months of age. The heart is greatly enlarged and the cardiothoracic ratio is 10.3/14.4 or 71 per cent. The pulmonary artery segment is convex and the pulmonary vascular markings are diminished.

Fig. 8 (Case 3).—The pulmonary artery has been cut open exposing the dome-shaped stenotic pulmonic valve projecting into it. The valve opening measures 2 mm. in diameter.

CASE 3 (2357111).—A 9-month-old white girl had slight cyanosis, a precordial systolic murmur, and enlargement of the heart at birth (Fig. 5). The cyanosis soon disappeared and was not noticeable except when she cried. However, it recurred and by the fifth month could always be noted in the nail beds. From this time on it gradually spread to the palms, soles, mouth, and then was generalized but only slight in degree. However, during crying, cyanosis was moderate. Physical development was retarded. Electrocardiographic evidence of right ventricular hypertrophy was present in the seventh month (Fig. 6). The chest roentgenogram by the eighth month showed a greatly enlarged heart (Fig. 7).

In her last month of life, she had two attacks of paroxysmal dyspnea during which time cyanosis was marked. A protodiastolic gallop was heard at the apex of the heart. The murmur decreased in intensity from Grade IV to Grade II. There was no clubbing of the digits. On the day of death the mother noted that her child had a fever, two hours later the infant had a loose

*Post-mortem examination by Dr. Roberto Ortiz, Children's Memorial Hospital, Chicago, Ill.

bowel movement, and then a generalized convulsion lasting ten minutes. This was followed by respiratory distress and marked increase in the cyanosis. She was immediately brought to the hospital where the temperature was found to be 105° F. (rectal), cardiac rate 140, and respiration 40 per minute. The liver was enlarged 3 fingerbreadths below the costal margin but no pulsations were detected. The infant died forty-five minutes after admission.

Anatomic diagnosis* was: valvular pulmonic stenosis, dilated pulmonary artery, patent foramen ovale, right ventricular hypertrophy, atelectasis of the left lung, acute ulcerative colitis, and acute mesenteric lymphadenitis. The heart and aortic segment weighed 156 grams. The right side of the heart was markedly enlarged. The myocardium of the right ventricle measured 9 to 10 mm. in thickness. There was some narrowing of the distal portion of the outflow tract of the right ventricle. There was no ventricular septal defect. The pulmonic valve cusps were completely fused, resulting in a dome-shaped valve, projecting into the pulmonary artery and having a 2 mm. opening at its apex (Fig. 8). The pulmonary artery was dilated, and measured 3.9 cm. in circumference, 1 cm. above the stenosed valve. The right atrium was dilated and the foramen ovale was patent, measuring 0.8 by 0.2 cm. in diameter. The tricuspid valve was markedly thickened. The pulmonary artery ostium of the ductus arteriosus was patent but the ductus was obliterated at the aortic end.

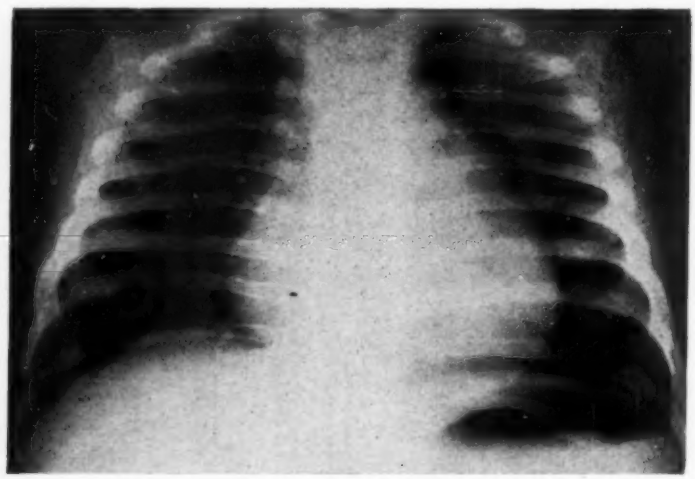

Fig. 9 (Case 4).—A chest roentgenogram taken at 5 months of age shows an enlarged heart with a cardiothoracic ratio of 7.0/13.4 or 52 per cent. The apex is upturned, and the pulmonary vascular markings are diminished.

CASE 4 (437692).—A 1-year-old white girl had a precordial systolic murmur at birth. The heart was progressively enlarged after the third month (Fig. 9). There was no cyanosis until the seventh month when it was noted on the patient's crying. The precordial murmur was loud (Grade IV) and a slight thrill was felt, both maximal at the base. An electrocardiogram (Fig. 10) showed prominent P waves and right ventricular hypertrophy.

The cyanosis gradually increased and by the eleventh month was constant, generalized, and moderate in degree. The liver was enlarged downward to the anterior iliac spine but did not pulsate. There was no clubbing of the fingers or toes. She was admitted because of a respiratory rate of 40 per minute. She improved after treatment with penicillin and oxygen, but later she had a severe paroxysm of dyspnea and died within twelve hours.

Anatomic diagnosis† was: valvular pulmonic stenosis, dilated pulmonary artery, patent foramen ovale, and right ventricular hypertrophy. The heart weighed 121 grams. The pulmonic valve cusps were fused into a single dome-shaped valve with a central perforation of 3 mm. The

*Post-mortem examination by Major Sproat.

†Post-mortem examination by Captain Wallace J. Redner, Medical Corps, United States Army.

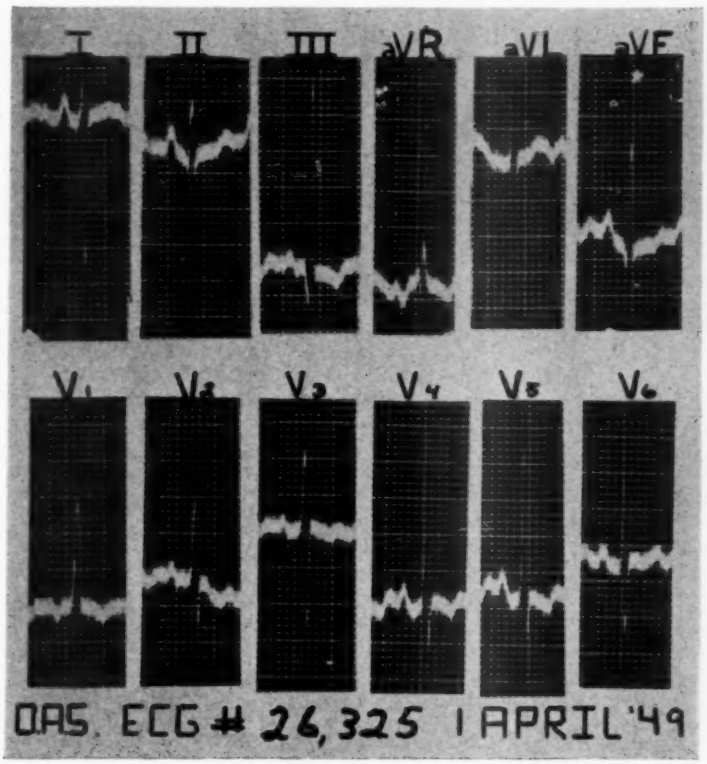

Fig. 10 (Case 4).—An electrocardiogram taken at the age of 7 months. There is a sinus tachycardia of 150 per minute present. The P-R interval is 0.12 second, the QRS width 0.07 second, and there is right axis deviation of plus 136 degrees. There are peaked P waves in Leads I and II, tall R waves in Lead III, inverted T waves in Lead III, diphasic T waves in Lead aV_F, tall R waves and inverted T waves in Lead V_1, and deep S waves persisting from Leads V_2 to V_6 with upright T waves in Lead V_6. The electrocardiographic diagnosis is sinus tachycardia, right ventricular hypertrophy, and questionable atrial hypertrophy.

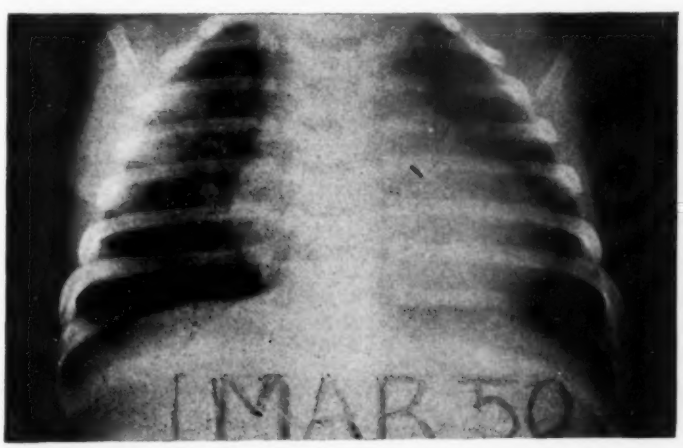

Fig. 11 (Case 5).—A chest roentgenogram taken at 3 months of age shows an enlarged heart and a cardiothoracic ratio of 7.2/12.1 or 60 per cent. The apex is upturned. There is slight fullness in the pulmonary artery segment and the vascular markings are diminished.

pulmonary artery was 1.5 cm. in circumference at the valve site and was dilated to 3.0 cm. in circumference above the valve. The other valves were normal. The foramen ovale was patent. The ductus arteriosus was closed. The right ventricle measured 1.0 cm. in thickness and the left ventricle was 0.5 cm. in thickness. There was no ventricular septal defect.

CASE 5 (2391017).—A 19-month-old white girl, who was slightly cyanotic at birth, had a loud precordial systolic murmur. In the third month, definite cardiac enlargement was shown by roentgenogram (Fig. 11) and there was only slight further increase in size during life.

The infant developed normally but the cyanosis progressively increased. It was constant but minimal in the lips and nail beds until the tenth month when it became generalized but only moderate in degree. Polycythemia and clubbing developed by the tenth month. She had frequent respiratory tract infections. The murmur was loudest in the left second and third intercostal spaces and by the fifteenth month a thrill was noted in this same area.

The electrocardiogram (Fig. 12) by the sixteenth month showed prominent P waves and right ventricular hypertrophy. By this time, her exercise tolerance was limited to 50 yards after which she would ask to be carried, but she never squatted.

Three weeks before she died, she had her first paroxysm of dyspnea. The liver was palpable 1 fingerbreadth below the costal margin and it did not pulsate. The systolic murmur had decreased to Grade II in intensity. The heart was enlarged (Fig. 13). During the next three weeks, she had several paroxysms of dyspnea which were relieved by morphine. She became markedly cyanotic with the slightest exertion, and without further change she died unexpectedly.

Anatomic diagnosis* was: valvular pulmonic stenosis, dilated pulmonary artery, patent foramen ovale, and hypertrophy of the right ventricle. The heart was markedly enlarged with predominance of the right ventricle. The pulmonic valve cusps (Fig. 14) were completely fused into a dome-shaped valve, containing a central perforation 0.8 mm. in diameter, which projected into a dilated pulmonary artery. The foramen ovale was patent. The ductus arteriosus was completely stenosed at the aortic end. There was no ventricular septal defect. The right ventricular wall was hypertrophied and equal in thickness to the left ventricle.

DIAGNOSIS

The diagnosis of pulmonic stenosis with open foramen ovale in infancy is based upon the symptomatology, the physical examination, and the characteristic electrocardiographic and roentgenologic findings, although other laboratory procedures may be required.

Symptomatology.—Cyanosis may be present at birth and may disappear only to recur either in the infant, the child, or the adult, depending on the severity of the condition. There are twenty-five cases in the literature,[3-5,14] with the diagnosis proved by post-mortem examination, in which age of onset of cyanosis is given. This was at birth in seven patients, between birth and 2 years of age in five, between the ages of 3 and 10 years in five, between 10 and 20 years in five, and over the age of 20 years in only three patients. Though Engle and Taussig[5] stress dyspnea as the primary symptom, it is the gradual increase in cyanosis that is characteristic in the infant. The onset of cyanosis preceded dyspnea in our cases. When dyspnea occurs in the infant, it is of the paroxysmal type, and it should be regarded as an ominous sign (Table I). When the infant or child can walk, there is a decreased exercise tolerance in the severer grades. Squatting is not characteristic of this malformation.

Physical Findings.—The heart is enlarged in most instances, and the chest may show a precordial bulge. A systolic murmur is heard along the left sternal border, and is loudest most commonly in the left second or third intercostal space

*Post-mortem examination by Captain Robert F. Ranson, Medical Corps, United States Army.

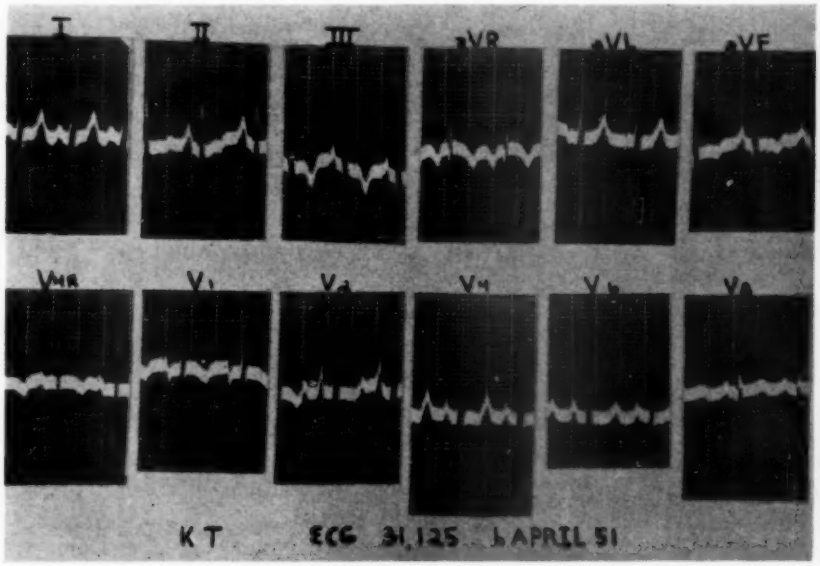

Fig. 12 (Case 5).—An electrocardiogram taken at the age of 16 months. There is sinus tachycardia of 140 per minute. The P-R interval is 0.12 second, the QRS width 0.06 second, and a right axis deviation of plus 120 degrees is present. There are prominent P waves in Lead II, flat T waves in Lead II, inverted T waves in Lead III and aV_F, tall R waves and inverted T waves in Leads V_{4R} and V_1, and diphasic QRS waves in Leads V_2 and V_4. These findings are diagnostic of sinus tachycardia and right ventricular hypertrophy. There is present questionable atrial hypertrophy.

Fig. 13.

Fig. 14.

Fig. 13 (Case 5).—A chest roentgenogram taken at 19 months of age. The heart is enlarged and the cardiothoracic ratio is 9.6/15.4 or 62 per cent. The pulmonary artery segment is full and the pulmonary vascular markings are diminished.

Fig. 14 (Case 5).—The dilated pulmonary artery has been opened to expose the stenotic pulmonic valve. The central perforation is 0.8 mm. in diameter.

and occasionally in the apical area. Its intensity varies, usually Grade III or sometimes only Grade II. Though Currens, Kinney, and White,[14] noted a high degree of correlation between the intensity of the murmur and the severity of the stenosis, this did not apply in our cases. All our infants had a high-grade stenosis, but the murmur varied from Grade II to Grade IV. In two of our patients (Cases 3 and 5), the murmur decreased in intensity from moderate to slight in their last month of life, just prior to the onset of paroxysmal dyspnea. Evidence of the low intensity of these murmurs was the frequent absence of a thrill and,

TABLE I. SUMMARY OF CLINICAL FEATURES

CASE NO.	1	2	3	4	5
Sex	F	F	F	F	F
Age at death (months)	3	4	9	12	19
Age at onset of cyanosis	Birth	Birth	Birth	7 months	Birth
Temporary loss of cyanosis	+	0	+	0	0
Onset of paroxysmal dyspnea (weeks before death)	2	3	4	1	3
Location of murmur (maximum intensity) (left intercostal space)	3	3-4	2-3	2-3	2-3
Grade of murmur*	3-4	3-4	4-2†	4	4-2†
Precordial thrill	0	+	0-+‡	+	0-+-0**
Enlarged liver	+	+	+	+	+
Pulsating liver	0	0	0	0	0
Clubbing of digits	0	0	0	0	+
Retarded physical development	+	0	+	0	0

0 = Absent.
+ = Present
*On basis of 1 to 6 (1 being very faint).
†Decrease in intensity terminally.
‡Absent at first examination.
**Absent at first and terminally.

TABLE II. SUMMARY OF LABORATORY FEATURES

CASE NO.	1	2	3	4	5
1. Roentgenogram of chest					
Cardiothoracic ratio (%)	67	56-65	62-72	52-59	60-66
Decreased vascular markings	+	+	+	+	+
Prominent pulmonary artery	+	0-+	0-+	+	+
Upturned apex	+	+	+	+	+
2. Blood					
Highest red blood cell count*	8.2	5.8	6.5	4.1	9.2
Highest hemoglobin value†	24.0	21.5	14.5	10.5	21.0
3. Electrocardiogram					
Prominent P waves	+	+	0-+	+	0-+
Right axis deviation in limb leads	+	+	+	+	0-+
Right ventricular hypertrophy in chest leads	+	+	+	+	0-+

+ = Present.
0-+ = Absent at first, later present.
*Millions per cubic centimeter.
†Grams per 100 c.c. blood.

when present, it was often difficult to detect.[15] The liver may be enlarged if the condition is severe. It has been described as pulsating, due to tricuspid incompetency. Though Engle and Taussig[5] stress this finding, it was not detected in our five cases. With cyanosis there eventually occurs polycythemia and clubbing.

Roentgenologic Examination.—Fluoroscopic and radiographic examinations are important in the diagnosis. The heart is usually enlarged with the cardiothoracic ratio between 50 to 70 per cent. (Table II.) It is the right atrium and right ventricle that enlarge. The pulmonary artery is dilated and therefore the "waist of the heart" is full in both the posteroanterior and the right anterior oblique views. The dilated pulmonary artery shows diminished or absent pulsations. The lung fields are clear; there is a decrease in the pulmonary vascular markings. These features form a characteristic picture.

Electrocardiographic Examination.—The tracing is characteristic except in the milder degrees of stenosis or early in the course of the severe types. Right axis deviation is present in the limb leads, and right ventricular hypertrophy is suggested by the tall R and inverted T waves in Leads II, III, and aV_F and the deep S wave in Lead aV_L. Characteristic are the tall, peaked, and prominent P waves in Lead II. A prolonged P-R interval may occur. Evidence of right ventricular hypertrophy is seen in the chest leads with a tall R wave followed by an inverted T wave on the right side of the precordium and a deep S wave persisting far over on the left side. Some have reported the finding of right bundle branch block, a manifestation of right ventricular hypertrophy, in these instances.

Cardiac Catheterization[17,43].—This may disclose the pathognomonic pressure gradient found in all varieties of pulmonic stenosis, low or normal pressure in the pulmonary artery, and high pressure in the right ventricle. Because of the stenosis, it may not be possible to pass the catheter through the valve into the pulmonary artery. This procedure is not without hazard as the plugging of the tiny opening in the pulmonic valve may result in the death of the patient. When right-to-left shunt is present, systemic arterial oxygen unsaturation is found.

Angiocardiography[18,28].—This procedure gives valuable diagnostic information but should not be undertaken lightly.[5] The significant findings include a delayed emptying of the dye from the right side of the heart. The films, after the first two to three seconds, show only slight changes and this is diagnostic of the slow emptying. The right-to-left shunt may be demonstrated by the early appearance of the dye in the left atrium and aorta, but there is not the dense opacification of the aorta as seen in an overriding aorta. Pooling of the Diodrast in the dilated pulmonary artery may occur.

DIFFERENTIAL DIAGNOSIS

1. *Congenital Isolated Pulmonic Stenosis.*—This malformation is known by a variety of names: isolated[19] or uncomplicated[13] or pure[20] pulmonic stenosis, congenital pulmonary stenosis,[22] congenital pulmonary stenosis with closed ventricular septum,[4] congenital pulmonary stenosis without overriding aorta,[23] pulmonary stenosis without septal defect,[24] pulmonary stenosis with intact interventricular septum,[14,27] stenosis of the pulmonary conus at the lower bulbar orifice (conus a separate chamber) and closed interventricular septum,[25] and congenital

pulmonary stenosis with closed cardiac septa.[21] This form should be differentiated from the variety with an open foramen ovale. Cyanosis, clubbing of the digits, and polycythemia are absent. Cyanosis may occur late in this malformation and it is then due to heart failure[26] or systemic venous stasis.[5] Dyspnea, especially upon physical exertion, is the characteristic symptom. Lesser degrees of pulmonic stenosis are completely asymptomatic and are to be suspected in the presence of a loud systolic pulmonic murmur. They may be confirmed by cardiac catheterization, which will reveal the gradient of pressure characteristic of all varieties of pulmonary stenosis.

The heart usually remains normal in size or the right ventricle hypertrophies slightly. The pulmonary artery is dilated. The vascular markings in the lungs are decreased or, in the less severe grades, are normal. The electrocardiogram is also normal in the lesser varieties but in the severer grades may show right axis deviation, right ventricular hypertrophy, or, occasionally, right bundle branch block. A systolic murmur is present and it is loudest in the left parasternal intercostal spaces, either second, third or fourth, and a thrill may be found.

2. *Tetralogy of Fallot.*—This is considered the commonest cause of morbus caeruleus. The heart usually remains normal in size and it has a characteristic shape showing a concavity of the pulmonary artery segment.[29] The pulmonary vascular markings are decreased. Cyanosis as well as clubbing and polycythemia are usually marked. Squatting is characteristic. The systolic murmur is more intense and located lower along the left sternal border (third and fourth intercostal spaces). The second pulmonic sound is pure (not reduplicated). A thrill is often absent. The electrocardiogram shows right axis deviation, prominent P waves in Lead II, and right ventricular hypertrophy. Cardiac catheterization studies may disclose the characteristic pressure gradient of pulmonary stenosis. The degree of elevation of the right ventricular systolic pressure is usually not as great as in pulmonic stenosis with open foramen ovale.[16] Due to the venous-arterial shunt into the aorta, there is arterial oxygen unsaturation. Angiocardiography reveals early opacification of the aorta.

3. *Ebstein's Anomaly of the Tricuspid Valve*[30].—Engle and Taussig[5] stress the resemblance of pulmonic stenosis with open foramen ovale to this rare, difficult-to-diagnose[41] malformation. The heart is enlarged, the pulmonary artery salient is not full, and the pulmonary vascular markings are poor. Angiocardiography may demonstrate the large right atrium and thin-walled right ventricle.

4. *Eisenmenger Complex*[31].—Cyanosis is late in onset. Cardiac catheterization may be diagnostic and disclose identical pressures in a systemic artery, the right ventricle, and the pulmonary artery.[32] Angiocardiography will show prompt emptying of the right heart and early visualization of the aorta.

5. *Tricuspid Atresia*[33].—The finding of left axis deviation in the electrocardiogram of a cyanotic patient with a congenital malformation of the heart is a valuable, though not pathognomonic,[34] aid. Angiocardiography may be useful.

6. Other conditions to be considered in the differential diagnosis include transposition of the aorta and pulmonary artery, truncus arteriosus, and cor pulmonale.

PROGNOSIS AND TREATMENT

A few patients with this malformation have lived to adulthood. A unique case reported by White and associates[40] was that of a woman who survived to the age of 75 years. However, if it is sufficiently severe to manifest itself in infancy, we are dealing with a serious and treacherous disease. Our experience has taught us the seriousness of paroxysmal dyspnea. When this occurs, the disease is far advanced, and unexpected and sudden death may occur.

Correct diagnosis is important for two reasons. First, in order to make plans to remedy it surgically when necessary. Second, the usual "blue baby" operations of Blalock and Taussig (subclavian-pulmonary artery anastomosis) and Potts and Smith (aorta-pulmonary artery anastomosis) are not helpful. They result in progressive heart failure, as the increased volume of blood returned to the left side of the heart can shut the foramen ovale. The right side of the heart thereby loses its safety or escape valve and progressive strain of the right side of the heart results.[7,39] Sellors[35] and Brock[36] have devised a direct approach operation. The stenosed valve is cut and dilated by an incision through the right ventricle. Indications for surgical intervention include (1) progressive heart enlargement,[37] (2) progressive electrocardiographic changes, (3) pressure in the right ventricle of 150 mm. Hg or greater, (4) paroxysms of dyspnea, and (5) systemic arterial oxygen saturation less than 20 per cent.

The younger the patient, the more serious is the operative risk. Postponement until the patient is at least 2 or, better, 5 years of age is desirable, but it may not be possible if the above-mentioned indications occur. Dammann[38] stated that thirty-three patients have been operated upon by the Brock technique at the Johns Hopkins Hospital. There were five deaths, four occurring while the patients were still on the operating table. The remaining patients have been greatly improved. Potts and Riker[6] reported thirteen patients who have had valvulotomy performed with one death occurring on the operating table. Included were five patients 1 year of age or less, two being only 23 and 39 days old. These authors state that the results following valvulotomy are often spectacular.

SUMMARY

Five cases of congenital valvular pulmonic stenosis with open foramen ovale occurring in infants and proved by autopsy are reported. The patients were all girls and their ages were 3, 4, 9, 12, and 19 months. This malformation may prove to be the second commonest cause of cyanotic congenital heart disease, only the tetralogy of Fallot being more frequent.

The syndrome in infants includes early cyanosis, often present at birth, which may clear for a short period, only to return. Polycythemia and clubbing of the fingers and the toes may follow the cyanosis. A precordial systolic murmur of slight to loud intensity is present. Dyspnea in these infants occurs in paroxysms and is a warning of approaching dissolution, which may be prevented by a timely surgical valvulotomy. The heart is enlarged and has a characteristic roentgenogram appearance of an upturned apex, a dilated pulmonary artery, and

avascularity of the peripheral lung fields. The electrocardiogram shows marked right ventricular hypertrophy and the P waves are prominent in Lead II.

This syndrome is to be differentiated from pure (isolated or uncomplicated) pulmonic stenosis and from the tetralogy of Fallot. The common "blue baby" operations of Blalock or Potts are not beneficial in pulmonic stenosis with open foramen ovale.

REFERENCES

1. Brown, J. W.: Congenital Heart Disease, ed. 2, London, 1950, Staples Press, Ltd., p. 179.
2. Abbott, M. E.: Atlas of Congenital Cardiac Disease, New York, 1936, American Heart Association.
3. Selzer, A., Carnes, W. H., Noble, C. A., Jr., Higgins, W. H., Jr., and Holmes, R. O.: The Syndrome of Pulmonary Stenosis With Patent Foramen Ovale, Am. J. Med. **6**:3, 1949.
4. Allanby, K. D., and Campbell, M.: Congenital Pulmonary Stenosis With Closed Ventricular Septum, Guy's Hosp. Rep. **98**:18, 1949.
5. Engle, M. A., and Taussig, H. B.: Valvular Pulmonic Stenosis With Intact Ventricular Septum and Patent Foramen Ovale, Circulation **2**:481, 1950.
6. Potts, W. J., and Riker, W. L.: Surgical Treatment of Pulmonary Stenosis With Intact Ventricular Septum, Arch. Surg. **62**:776, 1951.
7. Blalock, A., and Kieffer, R. F., Jr.: Valvulotomy for the Relief of Congenital Valvular Pulmonic Stenosis With Intact Ventricular Septum, Ann. Surg. **132**:496, 1950.
8. Joly, F., Carlotti, J., Sicot, J. R., and Piton, A.: Cardiopathies congenitales. II. Les trilogies de Fallot, Arch. d. mal. du. coeur **43**:687, 1950.
9. Wood, P.: Congenital Heart Disease, Brit. M. J. **2**:639, 693, 1950.
10. Selzer, A., and Carnes, W. H.: The Types of Pulmonary Stenosis and Their Clinical Recognition, Mod. Concepts Cardiovas. Dis. **18**:45, 1949.
11. Patten, B. M.: Closure of Foramen Ovale, Am. J. Anat. **48**:19, 1931.
12. Patten, B. M.: Developmental Defects at the Foramen Ovale, Am. J. Path. **14**:135, 1938.
13. Dow, J. W., Levine, H. D., Elkin, M., Haynes, F. W., Hellems, H. K., Whittenberger, J. W., Ferris, B. G., Goodale, W. T., Harvey, W. P., Eppinger, E. C., and Dexter, L.: Studies of Congenital Heart Disease. IV. Uncomplicated Pulmonic Stenosis, Circulation **1**:267, 1950.
14. Currens, J. H., Kinney, T. D., and White, P. D.: Pulmonary Stenosis With Intact Interventricular Septum, Report of Eleven Cases, Am. Heart J. **30**:491, 1945.
15. Counihan, T. B., Rappaport, M. B., and Sprague, H. B.: Physiological and Physical Laws That Govern The Clinical Appreciation of Cardiac Thrills, Paris, Abstracts, First International Congress of Cardiology **1**:83, 1950.
16. Maraist, F., Daley, R., Draper, A., Jr., Heimbecker, R., Dammann, F., Jr., Kieffer, R., Jr., King, J. T., Ferencz, C., and Bing, R. J.: X. The Physiological Findings in Thirty-Four Patients With Isolated Pulmonary Stenosis, Bull. Johns Hopkins Hosp. **88**:1, 1951.
17. Ordway, N. K., Levy, L., II, Hyman, A. L., and Bagnetto, R. L.: Pulmonary Stenosis With Patent Foramen Ovale, Am. Heart J. **40**:271, 1950.
18. Campbell, M., and Hills, T. H.: Angiocardiography in Cyanotic Congenital Heart Disease, Brit. Heart J. **12**:65, 1950.
19. Gøtzsche, H., Eskildsen, P., and Hansen, A. Tybjaerg: Isolated Pulmonary Stenosis, Acta med. Scandinav. **139**:431, 1951.
20. Greene, D. G., Baldwin, E. D., Baldwin, J. S., Himmelstein, A., Roh, C. E., and Cournand, A.: Pure Congenital Pulmonary Stenosis and Idiopathic Congenital Dilatation of the Pulmonary Artery, Am. J. Med. **6**:24, 1949.
21. Garrison, R. E., and Feldt, R. H.: Congenital Pulmonary Stenosis With Closed Cardiac Septa, Am. Heart J. **24**:685, 1942.
22. Lowance, M. I., Jones, E. C., Matthews, W. B., and Dunstan, E. M.: Congenital Pulmonary Stenosis, Am. Heart J. **35**:820, 1948.
23. Larsson, Y., Mannheimer, E., Moller, T., Lagerlof, H., and Werko, L. A.: Congenital Pulmonary Stenosis Without Overriding Aorta, Am. Heart J. **42**:70, 1951.
24. Pollack, A. A., Taylor, B. E., Odel, H. M., and Burchell, H. B.: Pulmonary Stenosis Without Septal Defect, Proc. Staff Meet., Mayo Clin. **23**:516, 1948.
25. Eakin, W. W., and Abbott, M. E.: Stenosis of Pulmonary Conus at Low Bulbar Orifice (Conus a Separate Chamber) and Closed Interventricular Septum, With Two Illustrative Cases, Am. J. M. Sc. **186**:860, 1933.

26. Selzer, A., Carnes, W. H., Noble, C. A., Jr., Higgins, W. H., Jr., and Holmes, R. O.: The Syndrome of Pulmonary Stenosis With Patent Foramen Ovale, Am. J. Med. **6**:3, 1949.
27. Potts, W. J., Gibson, S., Riker, W. L., and Leininger, C. R.: Congenital Pulmonary Stenosis With Intact Ventricular Septum, J. A. M. A. **144**:8, 1950.
28. Carson, M. J., Burford, T. H., Scott, W. G., and Goodfriend, J.: Diagnosis of Pulmonary Stenosis by Angiocardiography, J. Pediat. **33**:525, 1948.
29. Taussig, H. B.: Diagnosis of the Tetralogy of Fallot and Medical Aspects of the Surgical Treatment, Bull. New York Acad. Med. **23**:705, 1947.
30. Engle, N. A., Payne, T. P. B., Bruins, C., and Taussig, H. B.: Ebstein's Anomaly of the Tricuspid Valve, Circulation **1**:1246, 1950.
31. Selzer, A., and Laqueur, G. L.: The Eisenmenger Complex and its Relation to the Ventricular Septum, Arch. Int. Med. **87**:218, 1951.
32. Dexter, L.: Cardiac Catheterization in the Diagnosis of Congenital Heart Disease, Bull. New York Acad. Med. **26**:93, 1950.
33. Abrams, H. L., and Alway, R. H.: Tricuspid Atresia, Report of Three Cases and Evaluation of Diagnostic Criteria, Pediatrics **7**:660, 1951.
34. Kropp, I. G., and Grishman, A.: The Variability of the Electrocardiogram in Congenital Tricuspid Atresia, J. Pediat. **37**:231, 1950.
35. (a) Sellors, T. H.: Surgery of Pulmonary Stenosis, Case in Which Pulmonary Valve was Successfully Divided, Lancet **1**:988, 1948.
(b) Sellors, T. H., and Belcher, J. R.: Surgical Relief of Congenital Cyanotic Heart Disease, Late Results in 72 Cases, Lancet **2**:887, 1950.
36. (a) Brock, R. C.: Pulmonary Valvulotomy for the Relief of Congenital Pulmonary Stenosis, Report of Three Cases, Brit. M. J. **1**:1121, 1948.
(b) Brock, R. C.: The Surgery of Pulmonary Stenosis, Brit. M. J. **2**:399, 1949.
37. Blalock, A.: A Consideration of Some of the Problems in Cardiovascular Surgery, J. Thoracic Surg. **21**:543, 1951.
38. Dammann, J. F., Jr.: Congenital Malformations of the Heart Amenable to Surgery, South. M. J. **44**:915, 1951.
39. Brecher, G. A., and Opdyke, D. F.: The Relief of Acute Right Ventricular Strain by the Production of an Interatrial Septal Defect, Circulation **4**:496, 1951.
40. White, P. D., Hurst, J. W., and Fennell, R. H.: Survival to the Age of Seventy-Five Years With Congenital Pulmonary Stenosis and Patent Foramen Ovale, Circulation **2**:558, 1950.
41. Soloff, L. A., Stauffer, H. M., and Zatuchni, J.: Ebstein's Disease. Report of the First Case Diagnosed During Life, Am. J. M. Sc. **222**:554, 1951.
42. Abrahams, D. G., and Wood, P.: Pulmonary Stenosis With Normal Aortic Root, Brit. Heart J. **13**:519, 1951.
43. Grissom, R. L., Campbell, J. A., Selverstone, L. A., Fisher, D. L., and Donovan, D. L.: The Diagnosis of Congenital Stenosis of the Pulmonic Valve With Associated Auricular Septal Defect, Studies in Medicine. A Volume of Papers in Honor of Robert Wood Keeton, Springfield, Ill., 1951, Charles C Thomas, Publisher, p. 151.

PATENT DUCTUS ARTERIOSUS WITH PARTIAL REVERSAL OF THE SHUNT

A Study of Two Cases

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UNCOMPLICATED patent ductus arteriosus is associated with a continuous flow of blood from aorta to pulmonary artery at all phases in the cardiac cycle. The direction of this flow is dependent on the higher systolic and diastolic pressures in the aorta as compared with the pulmonary artery. The pressure gradient between the two vessels is greater in systole so that a continuous murmur with systolic accentuation is typical of patent ductus arteriosus. In isolated cases of patent ductus the pulmonary artery pressure becomes raised to such a degree that intermittent or complete reversal of the shunt is possible.[1] Under such circumstances, the clinical findings may alter with disappearance of the typical machinery murmur, and difficulty may be experienced in establishing the presence of a patent ductus arteriosus by clinical means alone.

In this paper the clinical presentation of two cases of patent ductus arteriosus with a partial reversal of the shunt is described and the results of cardiac catheterization, angiocardiography, oximetry, dye dilution studies, and simultaneous right brachial and femoral artery blood oxygen analyses are reported.

CLINICAL DATA

Case 1.—A 16-year-old white girl had complained of shortness of breath since childhood. There was no history of maternal illness during pregnancy, which was the first, and the labor was normal. A murmur over the heart was heard soon after birth. Further details of early infancy were lacking because the patient's mother was dead. The child started school at the age of 7 years but was never able to compete in any form of sport because of breathlessness on effort. Her effort tolerance became progressively worse so that at the time of examination it was limited to walking 200 to 300 yards. She had never been blue, and there was no history of rheumatic fever or of other serious childhood illness.

On examination the patient was a well-nourished normally developed young woman. There was some crowding of the upper teeth associated with a high and narrow palate. Pertinent findings were restricted to the cardiovascular system. The pulse rate was 90, the rhythm regular, and the pulse was collapsing in quality. The blood pressure was 120/50 mm. Hg. The jugular venous pressure was not raised and there were no signs of congestive failure. The maximum cardiac impulse was in the fifth intercostal space in the anterior axillary line and was abrupt and

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forceful in quality. In addition a systolic thrust and a diastolic shock were palpated in the left third intercostal space. A loud first sound was heard at the apex and the second heart sound at the pulmonary area was loud and split. A blowing systolic murmur (Grade III)[2] was loudest in the left parasternal region and a high-pitched diastolic murmur (Grade II) was maximal over the third left intercostal space. There was a presystolic murmur at the apex. No Gibson murmur could be heard.

Laboratory Data.—The hemoglobin was 14.5 Gm. per cent; white blood count 8,000 per c.mm. Sedimentation rate was 10 mm. in one hour (Westergren).

Fluoroscopy.—The cardiothoracic ratio was 54 per cent. There was a well-marked localized enlargement of the pulmonary artery segment, and the hilar shadows were prominent and pulsated freely on screening (Fig. 1). The aortic knuckle was small. The retrosternal space was almost completely occluded in the right anterior oblique view.

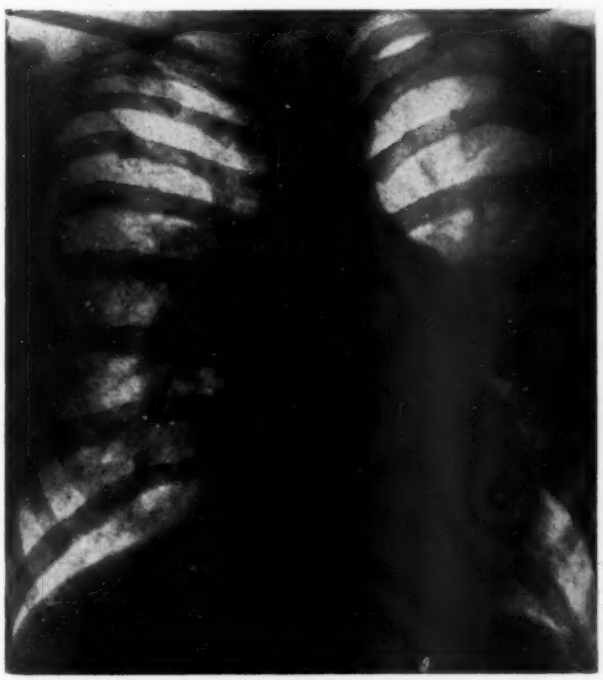

Fig. 1.—Posteroanterior view of chest in Case 1.

Electrocardiography.—An R/S ratio in V_1 of three (upper limit of normal not greater than one[3]) was suggestive of right ventricular hypertrophy. The high voltage R waves over the left chest were possibly related to left ventricular hypertrophy (Fig. 2).

Phonocardiography.—A mid-diastolic murmur with presystolic accentuation was demonstrated at the apex, and systolic and early diastolic murmurs were present down the left sternal border (Fig. 3). The configuration of the murmurs in the left sternal region did not resemble those commonly found in patent ductus arteriosus.

Cardiac Catheterization.—The results obtained by cardiac catheterization are shown in Table I.

There was marked hypertension in the pulmonary artery (90/70 mm. Hg) and right ventricle (90/5 mm. Hg). The right auricular pressure was normal.

Blood from the pulmonary artery showed a significantly higher oxygen content than that from the right ventricle, and the oxygen saturation in the right ventricle was significantly higher than that in the right auricle. These results could have been due to a patent ductus arteriosus

with marked pulmonary incompetence, a high ventricular septal defect (right ventricular samples not taken in the direct stream of the shunt), or a combination of a patent ductus arteriosus with a high ventricular septal defect.

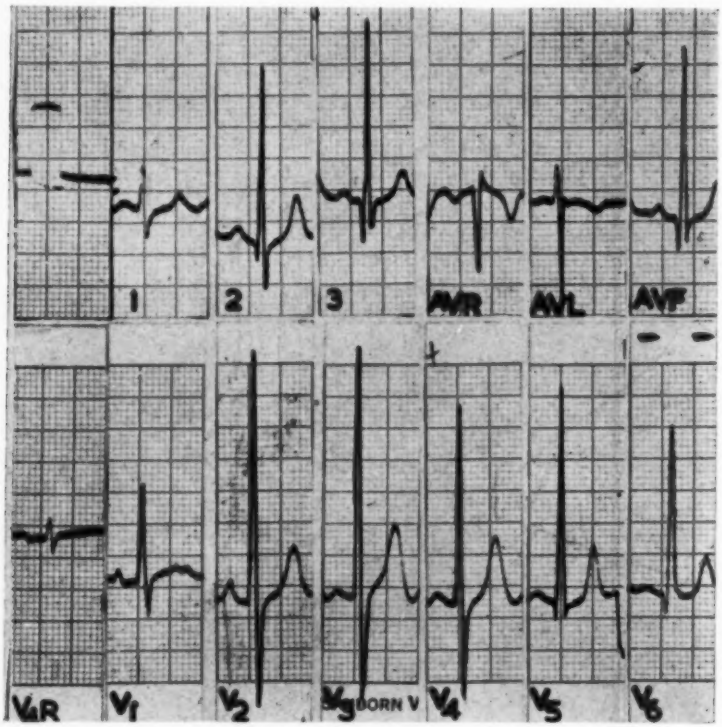

Fig. 2.—Electrocardiogram in Case 1 (retouched).

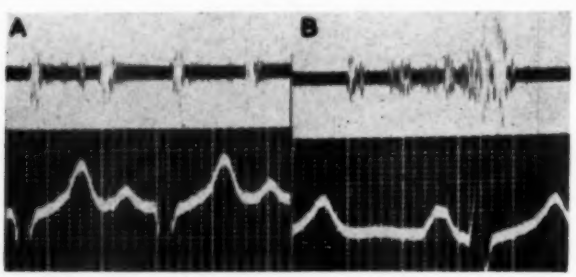

Fig. 3.—Phonocardiogram in Case 1. *A*, Pulmonary area. *B*, Mitral area.

*Oximetry**.—The resting arterial oxygen showed 93 per cent saturation in both ears. However, while it fell on effort to 84 per cent in the left ear there was no change in the right ear. This suggested a right-to-left shunt occurring after effort and affecting only the left carotid artery. A patent ductus arteriosus with the pulmonary pressure exceeding the systemic pressure after effort is the only anomaly which could produce such a result.

Dye Dilution Studies.—The technique and interpretation of results were as described by Nicholson and associates.[4] Evans blue (T.1824) in 0.5 per cent concentration was injected into the left external jugular vein and the apparent change in percentage oxygen saturation was re-

*Waters-Conley absolute reading oximeter.

TABLE I. CARDIAC CATHETERIZATION FINDINGS IN CASE 1

SITE	PRESSURE mm. Hg*		O_2 CONTENT (VOL. %)	O_2 % AGE SATURATION
	SYSTOLIC DIASTOLIC	MEAN		
Left pulmonary artery	90/70		15.45	87.6
Main pulmonary artery		78	15.47	87.6
High right ventricle	90/5		14.43	81.9
Low right ventricle	90/5		14.19	80.5
High right auricle	9/3		11.86	67.3
Mid right auricle		5	11.68	66.3
Low superior vena cava			12.62	71.6
Mid superior vena cava			12.29	69.7
Capacity			17.63	—
Arterial saturation		(Oximeter)		93.0

*All pressure readings from a point 5 cm. posterior to the angle of Louis.

corded with an oximeter on the left ear and subsequently on the right ear. The time from the injection of the dye to its appearance at the ear is known as the "appearance" time; from this point to the time of maximal concentration is called the "build-up" time, and finally the period from the maximal concentration point to the time when no further change occurs is the "disappearance time." In normal subjects the increase in concentration of the dye (build-up time) and its decrease in concentration (disappearance time) result in smooth curves. A venous to arterial shunt is capable of causing a short appearance time and the build-up time is broken into "primary" and "secondary" curves. The early appearance time and the primary curve are due to the venous-to-arterial shunt while the secondary curve represents the passage of dye through the normal circulatory paths.

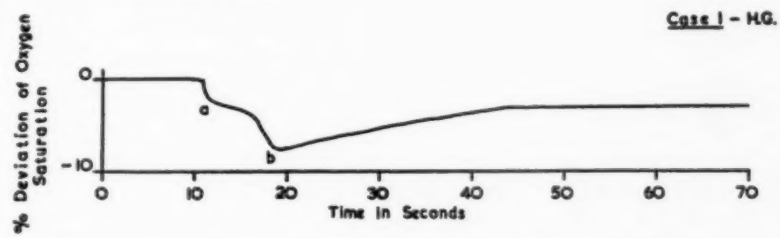

Fig. 4.—Dye dilution study in Case 1 showing the division of "build-up" curve into two waves (*a* and *b*) and a prolonged "disappearance" time (recorded on left ear).

The results in our case (Fig. 4) showed an appearance time of the dye at the lower limits of normal.[4] The build-up curve had a primary and a secondary wave, the apex of the second wave occurring at a normal time. The time taken for disappearance of the dye was prolonged. The short circulation time and the shape of the primary curve were suggestive of a venous-to-arterial shunt. This shunt was interpreted as being due to the passage of some dye from the pulmonary artery to the aorta and thence to the left carotid artery through a patent ductus arteriosus. The slow decline of the concentration curve (that is, prolonged disappearance time) is typical, in the absence of cardiac failure, of a left-to-right shunt. Pulmonary regurgitation, which was suspected on other grounds, may also have been a contributory factor. The procedure was repeated with the oximeter on the right ear, and a double-peaked primary curve, though much less marked, was again demonstrated. The occurrence of a right-to-left shunt through a septal defect would be expected to cause identical dye dilution curves in both ears. The demonstration, in this case, of a double-peaked primary curve more marked in the left than in the right ear suggested

that there was a larger quantity of venous blood going to the left ear as compared with the right ear. Such a result is to be expected if retrograde flow of blood occurs from pulmonary artery to aorta through a patent ductus arteriosus. This interpretation was compatible with the findings of the blood oxygen studies.

Progress.—A ventricular septal defect with pulmonary regurgitation could have explained the clinical and cardiac catheterization findings except for the high peripheral pulse pressure. However, as the dye dilution and oximetric studies were very suggestive of a patent ductus arteriosus with a bidirectional shunt, thoracotomy was advised. At operation a very short wide patent ductus ($\pm$ 1.5 cm. in diameter) was exposed. Because of technical difficulties it was only partially ligated with tape.

Two months after operation the patient was feeling well and was much less breathless on effort. The blood pressure was 120/80 mm. Hg and the pulse was not collapsing in nature. A typical continuous machinery murmur of patent ductus arteriosus was now heard over the pulmonary area. The early diastolic murmur down the left sternal border was much softer than previously and the mid-diastolic murmur at the apex had disappeared.

CASE 2.—*Clinical Data.*—The second case, a 34-year-old white woman, was admitted to hospital because of progressive breathlessness. The patient was a deaf mute and the relevant history was obtained from her private doctor. A murmur had been heard in the heart shortly after birth, and the child had always been delicate. Although she had never participated in any form of outdoor sport she was able to carry out household duties. She had always tired easily and in the weeks prior to her admission to hospital had complained of breathlessness on exertion and of pain in the right hypochondrium. Cyanosis had never been noted. A history of maternal illness during pregnancy was not obtained. No detailed history of childhood development or of past illnesses could be elicited.

On examination the patient, although deaf and dumb, was alert and intelligent. She was extremely small and thin (weight, 65 pounds). Although in congestive cardiac failure there was little orthopnea. Cyanosis of moderate intensity was present, especially in the extremities, and was more marked in the toes than in the fingers, although the lower limbs were as warm as the arms. The veins in the neck were pulsatile and engorged with the patient at an angle of 30 degrees to the horizontal. There were no crepitations at the lung bases but the liver was enlarged and tender. There was no peripheral edema. The pulse rate was 90 per minute and the rhythm was regular. The pulse was collapsing in quality (blood pressure, 160/75 mm. Hg). The chest wall showed a pigeon-shaped deformity and the heart was clinically enlarged. There was a palpable systolic thrust and a diastolic shock in the third left intercostal space 1 inch from the midline. In addition a forceful epigastric impulse was present. There were no thrills. On ausculation there was a systolic murmur (Grade II) and a widely split second sound at the aortic area. In the pulmonary area a systolic murmur (Grade III) and a soft blowing decrescendo diastolic murmur was present. The diastolic murmur reached maximal intensity in the third left intercostal space about 1.5 inches from the midline and was increased by forced expiration. At the apex a soft systolic murmur and an early diastolic murmur, which was conducted from the base, were audible. A low-pitched mitral diastolic murmur could occasionally be heard in the left lateral position. At no time was the machinery murmur of patent ductus arteriosus heard.

The only other findings of note were some patches of pigment on the retinae, probably of congenital origin.

She responded well to bed rest, digitalis leaf, mercurial diuretics, and a salt-free diet. When she had recovered from the congestive failure, the investigations listed below were carried out.

Laboratory Data.—Hemoglobin was 12 Gm. per cent; white blood count was 6,300 per c.mm. Sedimentation rate was 1 mm. in one hour (Westergren), and the urinalysis was normal.

Fluoroscopy.—The cardiothoracic ratio was 57 per cent. The pulmonary artery segment was markedly enlarged (Fig. 5). On screening the aortic and pulmonary artery pulsations were increased and both ventricles contracted vigorously. In the right anterior oblique view there was a prominence of the pulmonary arc and in the left anterior oblique view there was enlargement of both left and right ventricles.

Electrocardiography.—A delayed intrinsicoid deflection with large R waves and an R/S ratio of 1.91 in Lead V_1 were suggestive of right ventricular hypertrophy.[3] The T-wave inversion over the left chest, though probably a digitalis effect, may have been due to associated left ventricular enlargement (Fig. 6).

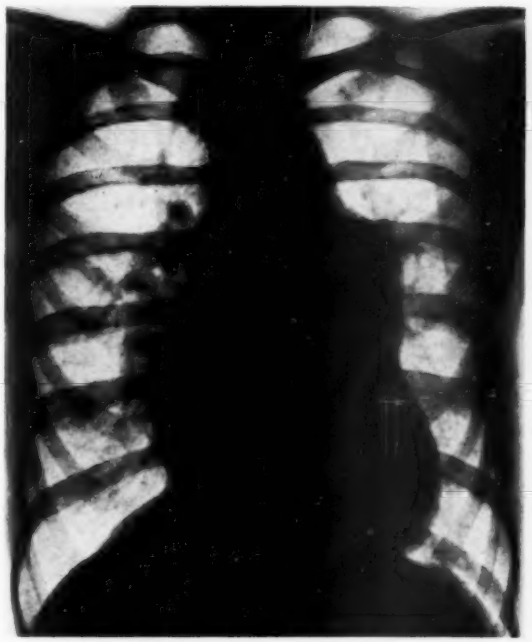

Fig. 5.—Posteroanterior view of chest in Case 2.

Phonocardiography.—The auscultatory findings were confirmed except for the mid-diastolic murmur at the apex which could not be demonstrated.

Cardiac Catheterization.—The results of cardiac catheterization are recorded in Table II.

TABLE II. CARDIAC CATHETERIZATION FINDINGS IN CASE 2

SITE	PRESSURE mm. Hg*		O_2 CONTENT (VOL. %)	O_2 % AGE SATURATION
	SYSTOLIC DIASTOLIC	MEAN		
Left pulmonary artery	135/53	88	6.93	43.0
Right pulmonary artery	144/86	98	6.74	42.0
Main pulmonary artery	150/80		7.33	45.6
Right ventricle (conus)	150/8	55	6.02	37.5
Right ventricle (low)	145/8		5.89	36.7
High right auricle	8/4	6	7.03	43.8
Low right auricle			6.36	39.6
Inferior vena cava			5.08	31.6
Superior vena cava			6.88	42.8
Right brachial artery	130/55†		9.5	59.2
Right femoral artery			8.16	50.8

***All pressure readings from a point 5 cm. posterior to the angle of Louis.**
†Sphygmomanometer reading.

There was marked hypertension in the pulmonary artery (150/80 mm. Hg) and a simultaneous right arm blood pressure, using a sphygmomanometer, was 130/55 mm. Hg. Recorded by different techinques these two pressures are not strictly comparable but do suggest that the pressure in the pulmonary artery may have been greater than the systemic pressure during all phases of the cardiac cycle at the time of the observation. (Blood oxygen analyses, however, showed the presence of a shunt of blood from aorta to pulmonary artery.) The systolic and diastolic pressures in the right ventricle were raised (150/8 mm. Hg).

Blood studies showed a significantly higher oxygen content in samples taken from the pulmonary artery as compared with the right ventricular blood. This result was strongly suggestive of a patent ductus arteriosus. The oxygen content of blood taken from the right brachial artery was 1.36 vol. per cent higher than that in a simultaneous femoral artery sample. An even greater difference (2.95 vol. per cent) was obtained on a subsequent occasion.

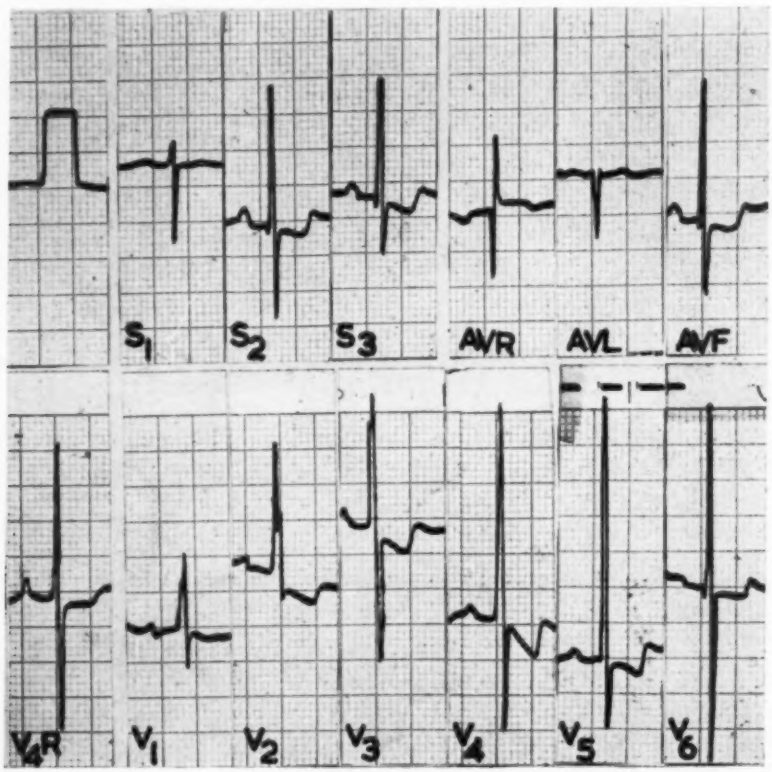

Fig. 6.—Electrocardiogram in Case 2 (retouched).

Oximetry.—The resting arterial oxygen saturation was the same in the two ears. On effort it fell 2 per cent in the right ear and 4 per cent in the left ear. The oxygen saturation rose normally on oxygen administration.

Dye Dilution Studies.—The technique was the same as in Case 1, except that the left median basilic vein was used for the injection of the dye. The build-up curve in the left ear consisted of two waves, as in Case 1 (Fig. 7). This result suggested the presence of a venous-to-arterial shunt. When the procedure was repeated with an oximeter on the right ear a double-peaked build-up curve was also obtained but was much less marked than on the left side. The delayed appearance time of the dye was consistent with the slow emptying of the right side of the heart which was subsequently shown at angiocardiography.

Angiocardiography.—Marked thickness of the right ventricular wall with a grossly dilated right ventricular outflow tract and main pulmonary artery was demonstrated. A large vessel was seen eight seconds after the injection of the dye arising from the commencement of the left pulmonary artery and terminating in the aorta (Fig. 8). This was taken to be a large patent ductus arteriosus. The delay in its filling could have been due to the slow circulation resulting from gross ventricular dilatation and pulmonic valvular incompetence.

Progress.—The patient was considered unsuitable for operation and was finally discharged on maintenance digitalis and mercurial therapy. On this regime she has led a comfortable, though restricted life in the six months since leaving hospital.

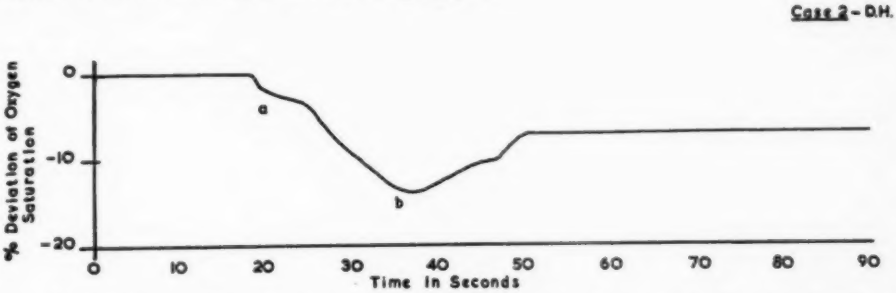

Fig. 7.—Dye dilution study in Case 2 with an oximeter on left ear. Delayed "appearance" time, double-peaked "build-up" curve and slow "disappearance" time.

Fig. 8.—Angiocardiogram in left anterior oblique view showing a grossly dilated right ventricular outflow tract and main pulmonary artery with a large patent ductus arteriosus arising from the commencement of the left pulmonary artery.

DISCUSSION

In spite of the increased flow through the pulmonary artery in cases of patent ductus arteriosus the pressure in this vessel may remain normal[1,5,6] or be moderately raised.[6] Rarely, however, the pulmonary pressure reaches such levels that

intermittent or complete reversal of the shunt may occur.[1,7-10] To diagnose the condition under these circumstances three criteria should be satisfied.

Features of uncomplicated patent ductus arteriosus must be present although the typical Gibson murmur is often absent. There must be a degree of pulmonary hypertension sufficient to allow for some reversal of the shunt. A lowering of the oxygen content must be shown in blood from the systemic arterial tree distal to the entrance of the patent ductus arteriosus into the aorta, that is, a regional distribution of the venous blood shunted from pulmonary artery to aorta.

Features consistent with patent ductus arteriosus were present in both our cases. Both showed a collapsing pulse. A localized heaving apex beat and some findings on electrocardiography and fluoroscopy suggested left ventricular hypertrophy. In addition the roentgenograms showed markedly pulsatile pulmonary arteries with a pulmonary artery segment sufficiently large and rounded in comparison to the other pulmonary vessels to suggest the cap of Zinn which is found in some cases of patent ductus arteriosus. Finally there was a higher oxygen saturation in blood samples from the pulmonary artery as compared with the right ventricle.

The degree of pulmonary hypertension demonstrated in both our cases at cardiac catheterization seemed sufficient to allow for a partial reversal of the shunt through the patent ductus arteriosus. Supportive clinical evidence for the presence of pulmonary hypertension was the systolic thrust and diastolic shock over the pulmonary artery segment and the early diastolic murmur of pulmonary incompetence down the left sternal border. Indirect evidence compatible with pulmonary hypertension was the demonstration of right ventricular enlargement by radiologic examination and by electrocardiography.

The diagnosis of some reversal of the shunt through a patent ductus arteriosus can however only be made with certainty in two ways. First, it may be possible to outline the ductus on angiocardiography as was done in Case 2. Such a finding is never seen in cases of uncomplicated ductus arteriosus. Second, and most important, the regional distribution of the venous blood shunted from the pulmonary artery into the aorta should be demonstrated. The major part of this blood passes down the descending aorta. There should be, therefore, a significantly lower oxygen content of blood in the lower limbs as compared with the right brachial artery.[15] Such a result was found in Case 2 where a difference in oxygen content of 2.95 vol. per cent was present. In addition, because of the proximity of the left carotid and subclavian arteries to the aortic opening of the patent ductus arteriosus it is possible to get some venous admixture of blood in both these vessels if there is reversal of the shunt. Oximetric measurements in Case 1 showed that there was no difference in the oxygen saturation in the two ears at rest. However the saturation fell from 93 per cent to 88 per cent on effort in the left ear while no change was recorded in the right ear. This result indicated the accentuation of the venous-to-arterial shunt on exercise. In the second case the results were similar though the difference was too slight to be confidently appraised.

Dye dilution studies substantiated the oximetric findings. A double-peaked build-up curve typical of a right-to-left shunt[4] was observed in the left ears of both cases while a similar, but much less marked, phenomenon was seen in the right ears. The findings in the right ears suggest that, with reversal of the shunt through a patent ductus arteriosus, enough turbulence or partial reversal of the flow occurs in the aorta during diastole to allow for some entry of venous blood into the innominate artery.

Taussig[11] doubts whether the amount of blood shunted from pulmonary artery to aorta in these cases is ever sufficiently large to cause clinical cyanosis. However several cases have been reported in which cyanosis was apparent.[6-8] In our Case 2 it was definitely present, being more marked in the feet than in the hands, and was not thought to be due to local factors. It was substantiated by the difference in oxygen saturation in the right brachial and femoral arteries. Such a finding, which has been previously noted by Pritchard and associates,[10] is to be expected only in cases with extreme degrees of pulmonary hypertension. In less severe cases it is necessary to demonstrate the regional distribution of venous blood by the methods which have been described above.

Because of the absence of the typical "machinery" murmur of patent ductus arteriosus in these cases, differential diagnosis may prove difficult. When the condition is acyanotic, both atrial and ventricular septal defects may be simulated. In neither is there a wide peripheral pulse pressure, and cardiac catheterization findings should exclude atrial septal defect. The cardiac catheterization results in patent ductus arteriosus with partial reversal of the shunt, and pulmonic incompetence may, however, be indistinguishable from those seen in ventricular septal defect (Case 1), as the pulmonic incompetence may allow for the regurgitation of arterialized blood into the right ventricle and thus give findings like those seen with ventricular septal defect. Such difficulties may be resolved by demonstrating the regional distribution of the shunted venous blood. Those cases of Eisenmenger's complex with an associated aortic incompetence may closely resemble reversed patent ductus arteriosus in which cyanosis has developed. A wide peripheral pulse pressure with the murmur of pulmonary incompetence at the heart base is to be expected in both cases. In addition fluoroscopic, electrocardiographic, and cardiac catheterization findings may be very similar. The two conditions can, however, be differentiated by demonstrating the regional distribution of the cyanosis in reversed ductus arteriosus. The only other anomaly associated with cyanosis more marked in the feet than in the hands is coarctation of the aorta of the infantile type where the lower limbs are supplied by the pulmonary artery via a patent ductus arteriosus.[11] This condition should show a normal pulse pressure. In addition, the regional distribution of shunted blood should be symmetrical, that is, both sides of the upper part of the body should have an equal oxygen saturation and this saturation should be higher than in the lower part of the body.[11] In contrast, partial reversal of the flow through a patent ductus arteriosus causes a regional but asymmetric difference in systemic arterial oxygen saturation, that is, the lower body has less well-saturated blood than the upper. But, in addition, there is a difference between the two sides of the upper

body in that the left carotid and subclavian arteries have a lower oxygen saturation than those on the right side.

The role of surgery in cases of patent ductus arteriosus with a bidirectional flow is debatable. Johnson and associates[1] feel that ligation of the ductus, by decreasing both pulmonary blood flow and pulmonary hypertension, should be beneficial. However, death has occurred in the only two reported cases with bidirectional shunts in which the patients have been submitted to operation.[1,10] Where the direction of the shunt seems to be mainly from right to left (as in Case 2) a sudden rise in pulmonary pressure can be expected immediately after ligation and operation seems to be contraindicated for this reason. Where the shunt is still mostly from left to right (as in Case 1), the position is more difficult and it is possible that operation may be beneficial. This was the experience in Case 1 despite the fact that the ductus arteriosus was only partially occluded at operation. However, the operative hazards are extreme. Crafoord[13] reports a mortality of two out of 266 uncomplicated cases as compared with eight deaths in the sixteen cases "with marked pulmonary hypertension" upon whom he has operated. He also reports a persistence of the pulmonary hypertension in some of the successful cases. The approach to operation in these cases should therefore be cautious.

The genesis of the marked pulmonary hypertension which occurs in isolated cases of patent ductus arteriosus is unknown. It has been shown by several authors that cases with marked pulmonary sclerosis at autopsy have had large ductuses.[1,7,8] However, Wood[6] could not demonstrate any constant relationship between the size of the shunt and the pulmonary artery pressure on cardiac catheterization, nor could Welch and Kinney[12] show increased pulmonary vascular sclerosis in twenty-five cases of significant ductus arteriosus. However, it seems possible that a large shunt causing an increase in pulmonary blood flow greater than three times the normal may lead to pulmonary hypertension[14] with the eventual development of pulmonary sclerosis. Under such circumstances the process may become irreversible.[15]

SUMMARY

Two cases of patent ductus arteriosus with intermittent reversal of the shunt are described. The bidirectional flow was demonstrated during life by cardiac catheterization, simultaneous right brachial artery and femoral artery blood oxygen analyses, oximetric and dye dilution studies, and by angiocardiography.

The clinical picture and laboratory findings to be expected in cases of ductus arteriosus with intermittent reversal of the shunt are presented and the extremely high operative mortality in such cases is stressed. Finally, the possible pathogenesis of the marked pulmonary hypertension is discussed briefly.

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REFERENCES

1. Johnson, R. E., Wermer. P., Kuschner, R., and Cournand, A.: Intermittent Reversal of Flow in a Case of Patent Ductus Arteriosus, Circulation **1**:1293, 1950.
2. Levine, S. A., and Harvey, W. P.: Clinical Auscultation of the Heart, Philadelphia and London, 1949, W. B. Saunders Company, p. 145.
3. Sokolow, M., and Lyon, T. P.: Ventricular Complex in Right Ventricular Hypertrophy as Obtained by Unipolar Precordial Limb Leads, AM. HEART J., **38**:273, 1949.
4. Nicholson, J. W., Burchell, H. B., and Wood, E. H.: A Method for Continuous Recording of Evans Blue Dye Curves in Arterial Blood and Its Application to the Diagnosis of Cardiovascular Abnormalities, J. Lab. & Clin. Med. **36**:974, 1951.
5. Dexter, L., Haynes, F. W., Burnell, C. S., Eppinger, E. C., Sosman, M. C., and Evans, J. M.: Studies of Congenital Heart Disease, Technique of Venous Catheterization as Diagnostic Aid in Patent Ductus Arteriosus, Tetralogy of Fallot, Ventricular Septal Defect and Auricular Septal Defect, J. Clin. Investigation **26**:561, 1947.
6. Wood, P.: Review of Clinical Aspects of Congenital Heart Disease in Light of Experience Gained by Means of Modern Techniques, Brit. M. J. **2**:539, 1950.
7. Chapman, C. B., and Robbins, S. L.: Patent Ductus Arteriosus With Pulmonary Vascular Sclerosis and Cyanosis, Ann. Int. Med. **21**:312, 1944.
8. Douglas, J. M., Burchell, H. B., Edwards, J. E., Dry, T. J., and Parker, R. L.: Systemic Right Ventricle in Patent Ductus Arteriosus, Report of Case With Obstructive Pulmonary Vascular Lesions, Proc. Staff Meet., Mayo Clin. **22**:41, 1947.
9. Dushane, J. W., and Montgomery, G. E., Jr.: Symposium on Cardiac Catheterization, Patent Ductus Arteriosus With Pulmonary Hypertension and Atypical Clinical Findings, Proc. Staff Meet., Mayo Clin. **230**:505, 1948.
10. Pritchard, W. H., Brofman, B. L., and Hellerstein, H. K.: Clinical Study in Reversal of Flow in Patent Ductus Arteriosus, J. Lab. & Clin. Med. **36**:974, 1950.
11. Taussig, H. B.: Congenital Malformations of the Heart, New York, 1947, The Commonwealth Fund, p. 489.
12. Welch, K. J., and Kinney, T. D.: Effect of Patent Ductus Arteriosus and of Interauricular and Interventricular Septal Defects on Development of Pulmonary Vascular Lesions, Am. J. Path. **24**:729, 1947.
13. Crafoord, C.: Meeting of Royal Society of Medicine, Brit. M. J. **1**:946, 1951.
14. Cournand, A.: Some Aspects of the Pulmonary Circulation in Normal Man and in Chronic Cardiopulmonary Disease, Circulation **2**:641, 1951.
15. Burchell, H. B.: Variations in the Clinical and Pathologic Picture of Patent Ductus Arteriosus, M. Clin. North America **32**:911, 1948.

MODIFICATION OF A VECTOR MODEL TO PROVIDE ACCURATE RECORDING OF MEAN VECTOR POSITIONS IN THREE PLANES OF SPACE

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THE MODEL devised by Grant and Estes, and described by them in their recent publication on vectorcardiography,[1] has been of great value in teaching and in practical use. By the use of a clear plastic cylinder representing the chest, and a rotating device consisting of a plastic disk and a pointer, representing a vector with its transitional place, it is possible to demonstrate, from the standard, unipolar extremity, and unipolar precordial leads, the spatial characteristics of any mean vector. The practical value of such a model is obvious, as it is very difficult in any other way to demonstrate the true spatial direction of the vector. A drawing and brief description of their original model is shown in Fig. 1. Subsequent simpler models have been constructed which do not involve the use of a light, as it is possible to visually project the transitional pathway to the chest wall if the diameter of the rotating disk closely approximates that of the "chest."

In our opinion there is one weakness in these models—the inability to mathematically record the degree of anterior or posterior, coronal or sagittal, deviation of the vector. Grant and Estes have attempted to do this by drawing a schematic "chest," and indicating the direction of the vector by the manner in which the transitional plane intersects the chest wall and by the appearance of the arrow drawn at the tip of the vector (Fig. 2). In practice, Grant and Estes and their students show the direction of the vector frontally by the use of the hexaxial reference system, while they indicate the other planes by the method shown in Fig. 2. We have shown in Fig. 3 the appearance of a vector analysis by this method, using only two "chests," as we were concerned only with the QRS and T vectors in this instance.

This method is completely satisfactory from a teaching point of view, but it has two disadvantages in everyday use. The first is the lack of a precise measuring system in the coronal and sagittal planes. The second, stemming directly from the first, is the inability to record degrees of change in successive cardiograms. In following patients over a period of time (such as hypertensive patients with a gradually changing vector pattern), it appeared to us that some method should be available which would enable us to mathematically record the direction of the vectors.

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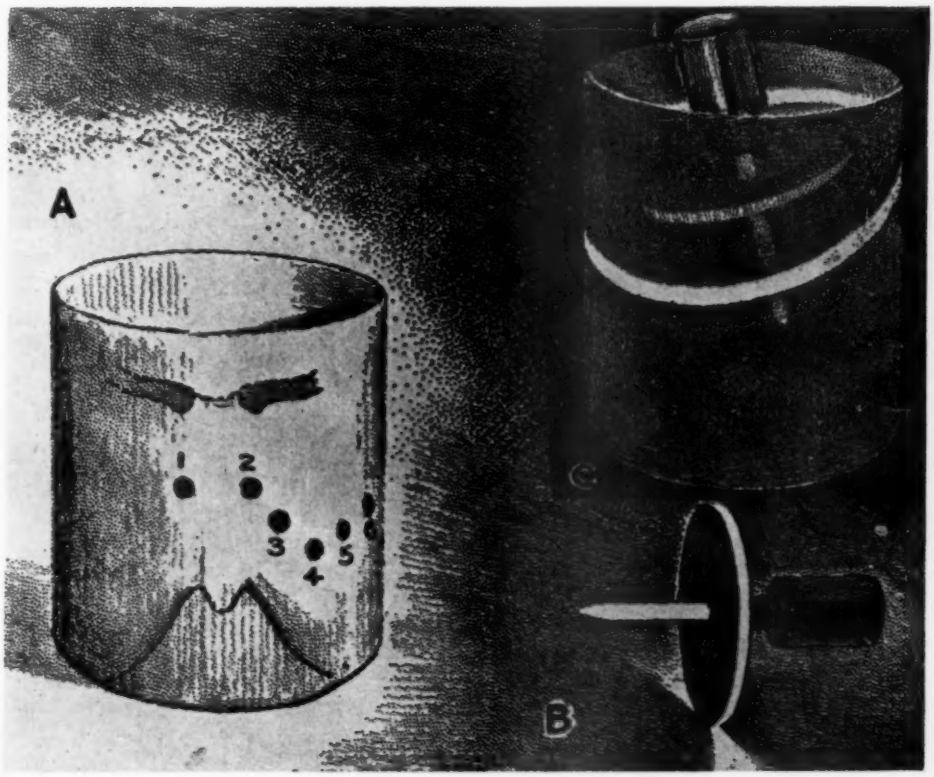

Fig. 1.—A model for demonstrating the distribution of positive and negative deflections on the chest for a given vector direction. The "vector" (*B*) (an ophthalmoscope with a Lucite rod and two cardboard disks mounted over the bulb) is held within the "chest" (*A*) (formed of cleared x-ray film). The circular beam of light it casts on the "chest," as shown in *C*, indicated the location of the transitional pathway for a given "vector" direction.

(This is the original Grant-Estes model as illustrated in their book, "Spatial Vector Electrocardiography." Reprinted by permission of The Blakiston Company, Philadelphia, Pa.)

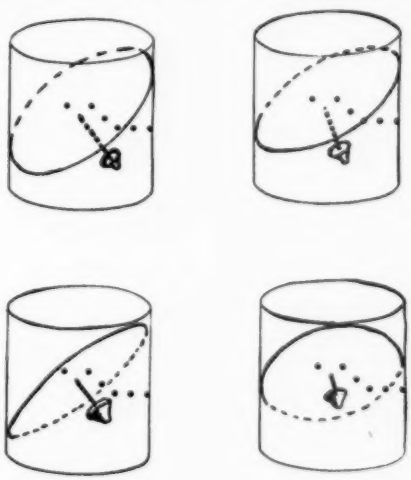

Fig. 2.—To illustrate the method used by Grant and Estes to indicate the direction of the mean spatial vector and the transitional plane.

We have accomplished this by mounting a degree scale in the bottom of the apparatus (for the coronal plane) and beside the "chest" (for the sagittal plane). Otherwise we have made no basic changes in the original Grant and Estes equipment. Our model is double-barrelled so that we can portray two vectors simultaneously. This made it convenient to mount the sagittal degree scale between the two "chests." All parts except the base and the scales are made of clear plastic. The rotating disks are connected to metal wheels beneath the wooden base so that they may be rotated without reaching inside the model. An attempt was made to control vertical shift of the vector from outside the model but this could not be done without making the whole apparatus too cumbersome. As now

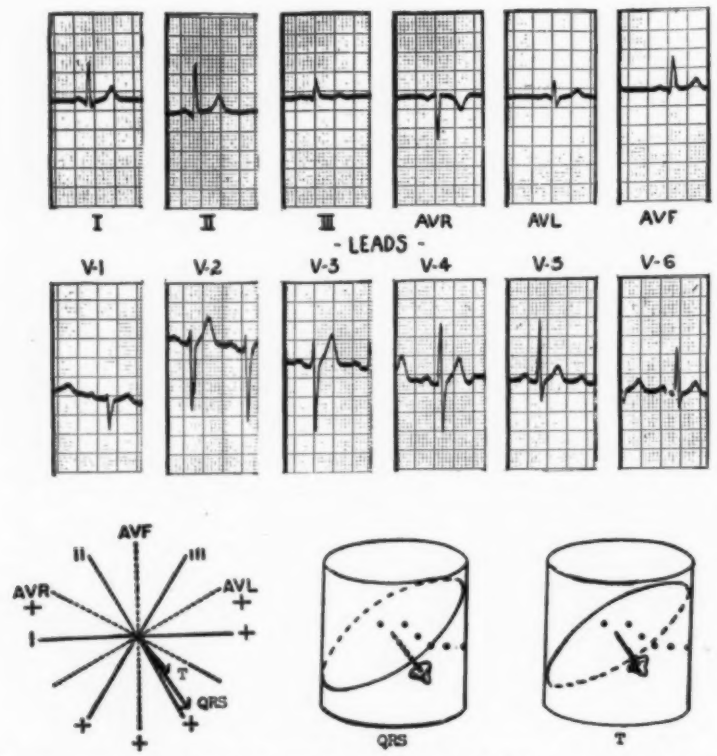

Fig. 3.—Vector analysis by the method of Grant and Estes, using only the QRS and T vectors in this illustration.

constructed the entire machine is only 6 inches high on a base 5 by 10 inches, easy to carry and to handle, and very sturdy. It was completely handmade, the construction being carried out by the junior author. The model is shown in Fig. 4.

In recording the frontal plane projection of the vector we use the conventional hexaxial reference system described by Grant and Estes. This has been etched on the plastic mounted behind the "chests" in our model, the positive portion of each lead line inscribed in red, the negative in white. Each vector is calculated exactly as described by them, and the model is used to show the spatial direction of this force. From this point our method differs from theirs. By looking

directly down through the "chest," the coronal projection of the vector can be determined and recorded. Originally the "0" point was placed on the left of the "chest," and anterior or posterior position was recorded up to 180 degrees. However, this method proved confusing, as a recorded anterior position of 175 degrees was actually only 5 degrees anterior from a line projected through the "chest" from side to side. For this reason we now have "0" reference points on each side, and record anterior or posterior position up to 90 degrees, indicating the side on which the vector is located, as, for instance, 75 degrees anterior on left, or "75° ant. L." The sagittal degree scale is similar to the coronal, except that the "0" points are vertically placed, and the degree of anterior or posterior displacement has to be qualified as to upper or lower anterior (or posterior) segment.

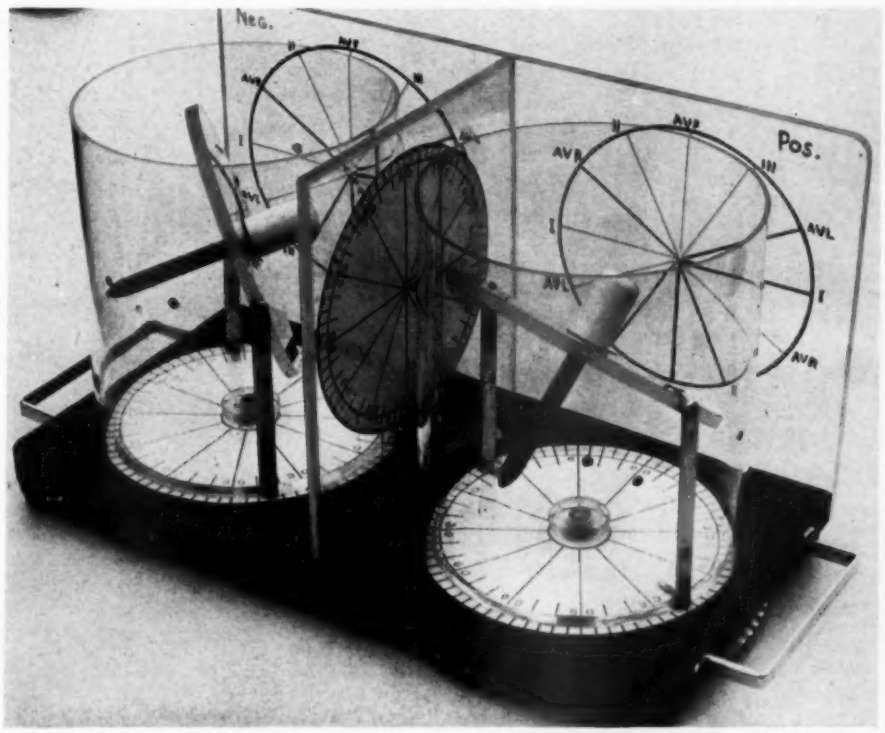

Fig. 4.—Our modification of the Grant-Estes model, photographed at an angle to show the degree scales mounted in the base and between the "chests."

The sagittal position is easily calculated by looking through the model from the side, the degree scale being placed vertically between the "chests." In practice we record the mean vectors from any cardiogram in the manner shown in Fig. 5 (same patient as in Fig. 3).

It is apparent that this method has no advantage from the purely visual viewpoint. In the hands of someone with a good artistic sense, the mean vector direction can be shown by the Grant and Estes method in a satisfactory manner. But there is no mathematical standard for comparison with progress cardiograms, or with other tracings. We feel that the addition of the coronal and

sagittal degree scales will enhance the usefulness of their ingenious apparatus. This will be particularly true if this or some similar mathematical scale method can be widely introduced.

To briefly illustrate our method we have shown in Fig. 6 the shift in the mean QRS vector occurring in a normal person between inspiration and expiration. This same method may be applied to all vectors and to any normal or abnormal cardiogram.

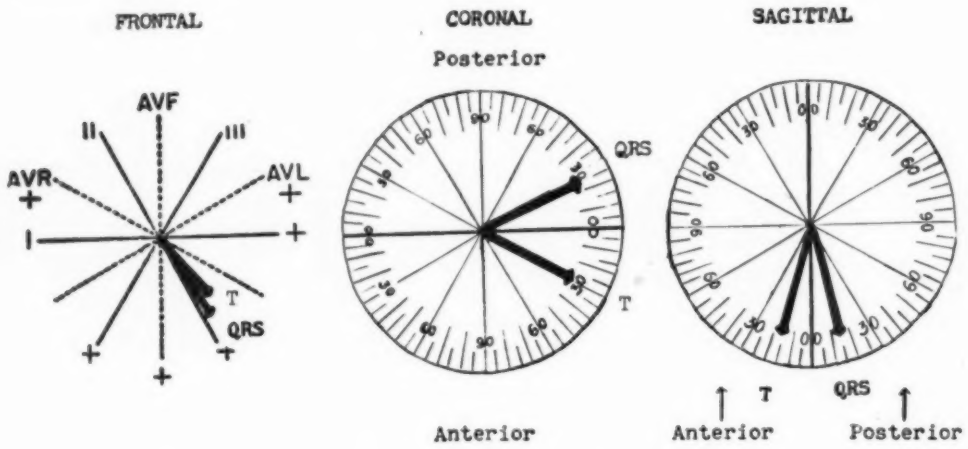

Fig. 5.—Vector analysis by our method.

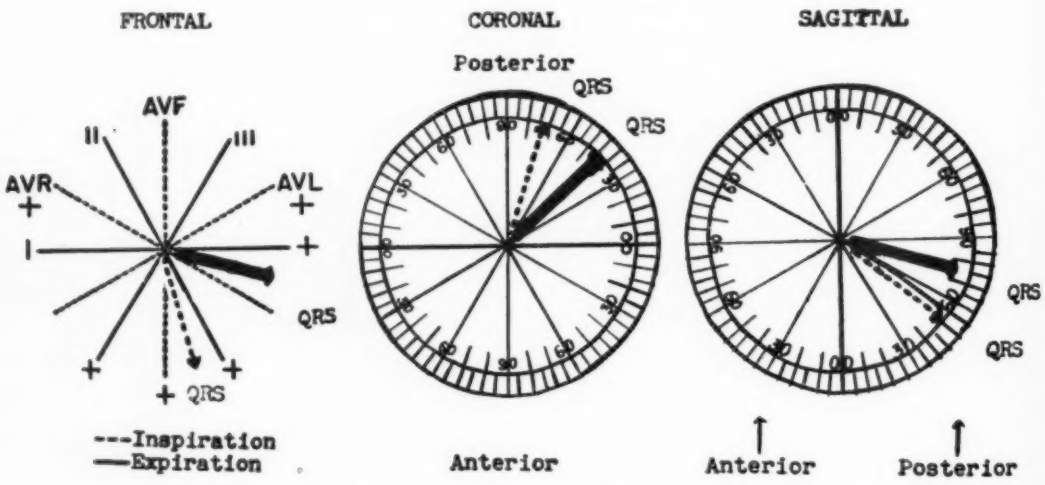

Fig. 6.—To illustrate the shift which occurs in mean QRS-vector direction in a normal patient between forced inspiration and forced expiration.

SUMMARY AND CONCLUSION

1. The vector model devised by Grant and Estes has been modified to provide precise recording of mean vector positions in the frontal, coronal, and sagittal planes.

2. This modification is of primary value in following the progress of mean vector changes in a series of cardiograms, but it will also be of increasing importance in establishing precise standards of normalcy in vector positions.

REFERENCE

1. Grant, R. P., and Estes, E. H.: Spatial Vector Electrocardiography, Philadelphia, 1951, The Blakiston Company.

A GEOMETRIC MODEL FOR DETERMINING THE DIRECTION OF MEAN SPATIAL VECTORS

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IT IS the purpose of this paper to describe a geometric model to determine the direction of certain vectors used in electrocardiography and to illustrate the use of this model. The geometric model may be used to represent vectors obtained by any method of vectorcardiography but this paper will be limited to the study of a modification of Grant's method because it makes use of leads now routinely used in electrocardiography.

Experience with Grant's original method[1-3] has proved interesting. However, in a number of instances we have been unable to visualize the mean spatial QRS-T angle with sufficient accuracy to be of clinical value, and we have found other individuals with the same problem. We believe that the ability to visualize a spatial angle from a two-dimensional drawing is somewhat subjective and requires that the user have an intuitive ability to visualize three-dimensional representations, a quality that is not equally possessed by all. This creates the problem of actually representing these vectors in space by means of a comparatively simple reference system which permits one to obtain objective and quantitative results. We believe the geometric model to be described fills this need.

DESCRIPTION AND USE OF GEOMETRIC MODEL

The procedure involved in the use of the model is based upon the determination of the frontal and horizontal plane projections of the spatial vector from which the direction of the responsible spatial vector is reconstructed in the model.

Construct a box 18 inches square consisting of top, bottom, and two opposite sides (Fig. 1). Before the sides are mounted to form the box, draw four concentric circles, 3 inches, 5 inches, 10 inches, and 15 inches in diameter on one of the sides. At 5-degree intervals around the perimeter of each circle, drill holes $\frac{5}{64}$ inch in diameter. This layout can be easily accomplished as follows: Using a 10-inch protractor, draw a circle and mark it at 5-degree intervals around the circumference. Draw radii from the center to each 5-degree mark. Draw additional circles, 3 inches, 5 inches, and 15 inches in diameter. With this marked side on top, stack the four sides, one upon the other, clamp them securely together, and drill holes around the circumference of each circle at 5-degree intervals through the stacked sides. Mark each hole around the anterior and posterior hemicircles from zero degrees on the left to 180 degrees on the right. Erect a

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narrow support exactly 9 inches high from the center of the model floor. The top of this support represents the center of the system. Two rods representing the spatial vectors are eventually attached here by means of a screw clamp, elastic band, or other similar device to hold the centers of the vectors in place. We used a small thin piece of rubber sheeting with a hole through it.

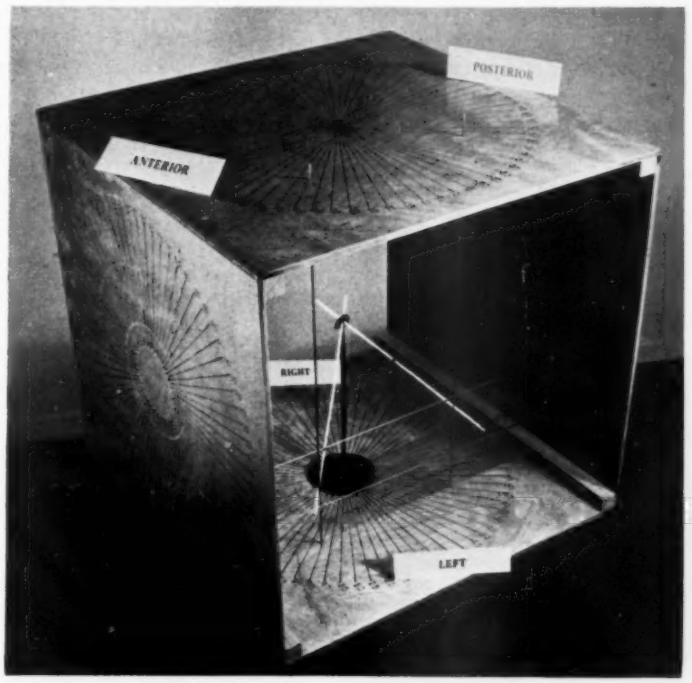

Fig. 1.—The geometric model. (For description see text.) In this photograph the following values were used. In the frontal plane the projection of the mean QRS vector is +50 degrees, the mean T vector +60 degrees, giving a frontal plane QRS-T angle of 10 degrees. In the horizontal plane, the projection of the mean QRS vector is 45 degrees posteriorly, the mean T vector 45 degrees anteriorly, giving a QRS-T angle of 90 degrees. In space the QRS-T angle measured with a protractor is 60 degrees.

The direction of the spatial vector is determined as follows: Observe the direction of the horizontal plane projection* of the spatial vector. We chose a modification of Grant's method to be described in the next paragraph for this purpose. Place a metal rod† 18.5 inches long and $\frac{5}{64}$ inch in diameter through the pair of holes in the top and bottom of the model which correspond to the degrees of rotation anteriorly or posteriorly of the horizontal projection of the vector. Observe the direction of the frontal plane projection of the spatial vector and place a metal rod 18.5 inches long through the pair of holes in the opposite sides of the model from front to back, which correspond to the degrees of rotation of the frontal plane vector. Then place a third rod, $\frac{1}{32}$ inch in diameter and 10 inches long, from the center of the model so that the third rod rests against

*As a matter of definition we shall call the plane of the precordial leads the horizontal plane. This plane is horizontal in the geometric model and is horizontal when the body is viewed in the upright position. However, it must be kept in mind that when the body is recumbent, the usual position for the electrocardiogram, the plane of the precordial leads, is really vertical.

†Very stiff wire or preferably steel rods, known by the trade name of drill rods, may be used.

both of the two rods previously placed. Whereas the third or diagonal rod must touch the first two rods, these first two rods need not touch each other. A spring clip may be used if necessary to hold the distal end of this vector rod in place against the rods it touches. This diagonal is the direction of the spatial vector. The selection of the circles (3-inch, 5-inch, 10-inch, or 15-inch) used to represent the frontal and horizontal plane projections should be chosen so that the rod representing the spatial vector can touch both of the other two rods within the confines of the model. How this should be done becomes apparent after a little experience with the use of the model.

The directions of the mean spatial QRS and T vectors can be determined and the spatial QRS-T angle can be measured directly with a protractor. Similarly the angle between the initial 0.04 second vector of the spatial QRS and the mean spatial QRS vectors can be determined. This method will permit the more precise estimation and study of these spatial angles to determine whether they are of any value as a routine clinical procedure.

METHOD FOR OBTAINING PROJECTIONS OF MEAN SPATIAL VECTOR

For this purpose Grant's method[1-3] was modified by the introduction of a more quantitative technique for obtaining the horizontal plane spatial vector projection. This involves measurement of the anteroposterior and transverse chest diameters, measurement of the positions of the transitional zone complexes on the anterior or lateral chest walls, and the use of a diagram drawn to scale in which the center of the vector system is assumed to be slightly anterior and to the left of the anatomic center of the chest for reasons covered in the discussion. We would like to say in advance, that while the method is tedious to describe, it can be performed in less than five minutes.

The chest dimensions are determined with an x-ray caliper. A rectangle with the anteroposterior and transverse chest diameters is drawn to a scale of one-half or one-fourth actual size (Fig. 2). The electrode position at which the deflection representing the vector in question is transitional in type* is noted and the distance from it to the nearest lateral chest wall is recorded with x-ray calipers. If the transitional deflection occurs at one or the other of the V_1 to V_4 positions, its location is marked upon the scale model rectangle along the anterior side. If such a deflection occurs at V_6 or V_{6R} it is considered to be on one of the lateral sides of the diagram in which case the distance of the V_6 electrode position from front to back is measured and marked accordingly on the rectangle. Because the chest usually is curving backward at the V_5 position, it is necessary to measure the location of V_5 in terms of distance from the left chest wall and also the distance posteriorly from the anterior chest wall as defined by the relatively flat

*In the average normal individual the transitional zone complex for the QRS is almost invariably found in the usual precordial Leads V_1 to V_6. Frequently the transitional complex for the T wave is found on the right anterior chest, in which case leads from V_{3R} to V_{6R} must be taken. If most of the precordial leads are transitional zone in type for the QRS or T it usually indicates that the mean spatial vector is pointing either upward toward the head or downward toward the feet, so that several of the V lead electrode locations lie in the transitional zone.

surface which exists from V_4 to V_{4R}. The measured position of V_5 is entered accordingly within the scale rectangle.

The center of the vector system is placed at the transverse level of V_2 and at an anteroposterior level five-twelfths of the distance from front to back. The reasons for this are covered in the discussion. Having drawn the scale rectangle, and marking the position of the transitional deflection as point T and the vector center as point C, draw a line from T to C. Next erect a perpendicular CD to line TC from point C. This is the direction of the horizontal plane projection of the spatial vector. Draw a line AB through the origin of the vector across the rectangle parallel to the front and back. Measure the angle θ between lines CD and AB. This angle θ gives the rotation of the horizontal plane projection of the mean spatial vector in question. The frontal plane projection of the spatial

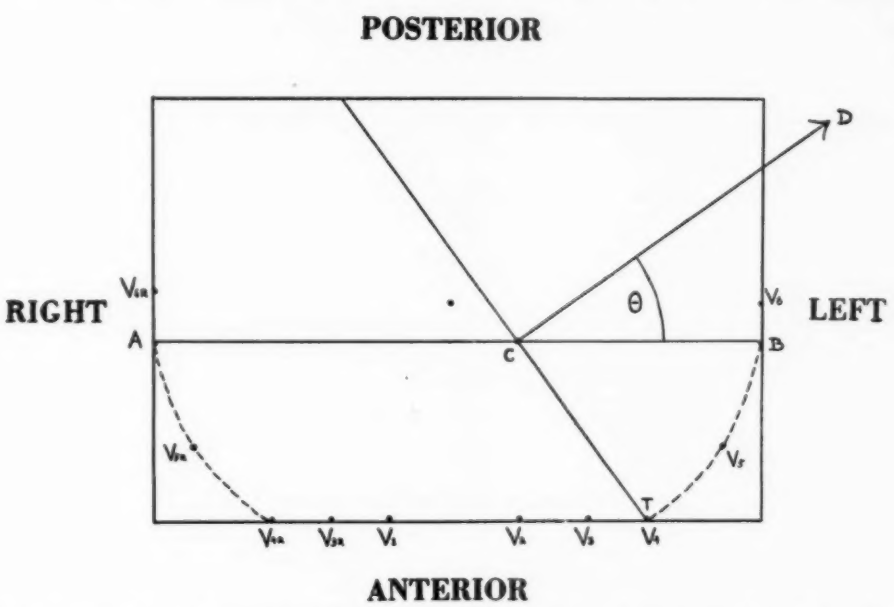

Fig. 2.—Scale model diagram used for determining direction of the horizontal plane projection of the spatial vector. In this diagram the transitional deflection was at V_4. (For explanation see text.)

vector is usually obtained by simple inspection of the six extremity leads as described elsewhere.[3,4] Occasionally in doubtful cases it may be necessary to measure the net algebraic areas of the deflections in the bipolar extremity leads and plot the frontal plane projection in the triaxial reference system. Having obtained the frontal and horizontal plane projections of the spatial vector, the direction of the responsible spatial vector is determined in the geometric model as described in the previous section.

RESULTS

As a preliminary study to illustrate the use of the model, the QRS-T angle in eight cases was determined. These cases were chosen from the periodic examination files of fifty healthy individuals free from detectable heart disease where a visualization of the spatial QRS-T angle by Grant's original method indicated that

it was rather wide. The actual results in these individuals, ranging in age from 35 to 56 years, are enumerated as follows: 60 degrees, 70 degrees, 70 degrees, 70 degrees, 60 degrees, 65 degrees, 75 degrees, and 65 degrees. These results suggest that the upper limit of normal for the spatial QRS-T angle of 50 degrees as set by Grant[3] may be exceeded in a significant proportion of the normal adult population. In all of our cases the frontal plane QRS-T angle was well within normal limits.

DISCUSSION

The method for obtaining spatial vectors which has been described here, as well as any other method of vectorcardiography, implies that certain assumptions underlying the Einthoven hypothesis are at least first approximations of the true conditions. These assumptions are not readily amenable to direct verification, and so far the exact degree to which the actual situations resemble the theory has never been quantitatively ascertained. This problem has been discussed elsewhere.[4] However, since the empirical use of vectorcardiography has been reported to be of value,[3-10] we believe that a thorough empirical study of the mean spatial QRS-T angle and other vector relationships is warranted. We have described here a reasonably accurate and objective method for a quantitative study of mean spatial vector relationships. Criteria for normal subjects can be determined and the deviation from these criteria in cases of established heart disease can be studied. If a quantitative system of electrode placement such as the cube[7] is used, the vectors may be determined quantitatively. With such a system it seems probable that a spatial ventricular gradient can be obtained by modifying the model so that a parallelogram can be constructed in space.

The use of precordial electrode positions for vectorcardiography requires some justification because of the proximity of the precordial electrode to the heart as contrasted with the distance to an extremity or back electrode. We felt that the use of a precordial electrode was justified because of Grant's studies of the heart's electrical field and, secondly, because Duchosal and Sulzer,[5] Grishman and Scherlis,[8] and Milnor and associates[9] have found that usually good contour resemblances of the precordial leads can be reconstructed from the horizontal plane loops recorded from electrodes distant to the heart.

The assumption was made that the electrical center of the heart, for the purpose of this study, in the average individual without cardiac enlargement is approximately behind the V_2 electrode position and $\frac{5}{12}$ the anteroposterior diameter from the anterior chest wall. The V_2 position was chosen because V_2 was usually near the anatomic center of the heart as seen in the posterior-anterior film. The figure $\frac{5}{12}$ was obtained as follows: It was found that the posterior border of the heart in the lateral recumbent film was usually about one-half the anteroposterior diameter of the chest from the anterior chest wall. The center of the muscle mass in the lateral film was usually one-third the anteroposterior diameter of the chest from the anterior chest wall. Therefore, to allow for the usual more posterior position of the electrically predominant left ventricle a mean between these two distances, namely $\frac{5}{12}$, was decided upon.

At one time it was hoped that Grant's method could be modified so as to use the electrode position of the posterior chest wall transitional zone deflection in addition to the usual anterior chest wall position. By joining these two positions with a line it was hoped that the axis perpendicular to the horizontal projection of the mean spatial vector could be more accurately determined. However, when using this method to study QRS-T angles it was found that the intersection of the two lines which joined the pairs of QRS and T transitional zone complexes occurred behind the anatomic position of the heart in a majority of cases. The possible reason or reasons for this finding require further study. Therefore, we felt this method of utilizing transitional type deflections on both anterior and posterior thoracic surfaces could not be recommended now.

SUMMARY

A geometric model for the objective determination of mean spatial vectors has been described. This instrument is applicable to the determination of vectors from any suitable system of electrode placement, such as a cube, tetrahedron, Grant's method, or the method described here.

REFERENCES

1. Grant, R. P.: The Relationship of Unipolar Chest Leads to the Electrical Field of the Heart, Circulation **1**:878, 1950.
2. Grant, R. P.: Spatial Vector Electrocardiography, a Method for Calculating the Spatial Electrical Vectors of the Heart From Conventional Leads, Circulation **2**:676, 1950.
3. Grant, R. P., and Estes, E. Harvey: Spatial Vector Electrocardiography, Philadelphia, 1951, The Blakiston Company.
4. Langner, P. H., Jr.: The Theory and Practice of Vector Analysis in Electrocardiography. Proceedings of the Medical Section of the American Life Convention, June 15, 1950.
5. Duchosal, P. W., and Sulzer, R.: La Vectocardiographie, Basel, Switzerland, 1949, S. Karger.
6. Duchosal, P. W., and Grosgurin, J. R.: The Spatial Vectorcardiogram Obtained by Use of a Trihedron and Its Scalar Comparison, Circulation **5**:237, 1952.
7. Grishman, A., Borun, E. R., and Jaffe, H. L.: Spatial Vectorcardiography: Technique for the Simultaneous Recording of the Frontal, Sagittal and Horizontal Projections, Am. Heart J. **41**:483, 1951.
8. Grishman, A., and Scherlis, L.: Spatial Vectorcardiography, Philadelphia, 1952, W. B. Saunders Company.
9. Milnor, W. R., Genecin, A., Talbot, S. A., and Newman, E. V.: Studies on the Validity and Applications of the Spatial Vectorcardiogram. Twenty-fourth Scientific Session, American Heart Association, Atlantic City, N. J., June 8-9, 1951.
10. (a) Abildskov, J. A., Jackson, C. E., Burch, G. E., and Cronvich, J. A.: The Spatial Vectorcardiogram in Right Bundle Branch Block, Circulation **3**:600, 1951.
    (b) Pantridge, J. F., Abildskov, J. A., Burch, G. E., and Cronvich, J. A.: A Study of the Spatial Vectorcardiogram in Left Bundle Branch Block, Circulation **1**:893, 1950.

A SIMPLE TECHNIQUE FOR REGISTERING THE DIRECTION OF ROTATION OF VECTORCARDIOGRAPHIC LOOPS

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THE INCREASING number of recent publications dealing with vectorcardiography suggests that the advantages peculiar to the method are becoming more widely appreciated. It is not within the scope of this paper to discuss these advantages nor the undeniable limitations of the vectorcardiographic approach. However, its place as a supplement to conventional electrocardiography and as an investigative tool seems assured.

Many different methods for recording vectorcardiograms have been developed, varying mostly in the selection of sites of placement of the recording electrodes. Whatever method is used, one records more or less comparable vectorcardiographic loops (sometimes called sÊ loops after Bayley[1]) as projected on various planes of the body. For each plane it is essential that one know the direction in which the QRS loop was inscribed to be able to interpret the record.

Heretofore there have been two principal ways to record the direction of rotation of the QRS loop. The first consists of having the operator observe the screen of the oscilloscope tube directly as the loop is being written. He then records his impression on paper for future reference. This has the disadvantage that the information is not made an inherent part of the vectorcardiogram itself, that is, it is not apparent upon looking at the record. A more serious difficulty lies in the fact that with small or complicated QRS loops it is sometimes very difficult or even impossible to make out the direction of inscription just by watching. Some investigators try to get around this by having several observers record their impressions independently and then come to a majority opinion[2]—a rather cumbersome but still not necessarily exact method. An expensive variation consists of the use of a high-speed moving picture camera to record the oscilloscope screen image.[2,3] Used by itself, this method does not produce a record which can be conveniently analyzed, nor can the record be readily incorporated into a clinical chart.

The second method, popular particularly with French-speaking authors, was first described in Germany in 1937 by Hollmann and Hollmann.[4] In this method the vectorcardiogram is recorded on film which is moving. By knowing the direction of motion of the film one can then determine the direction in which the loop was inscribed. This method involves the use of expensive photographic

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equipment and distorts the record for spatial analysis so that stationary-film vectorcardiograms must also be taken. A similar result may also be achieved by allowing the film to remain stationary but having the electron beam of the oscilloscope be deviated continuously in one direction during the inscription of the vectorcardiogram by an external sweep voltage applied to only one set of the oscilloscope's deflecting plates. Unfortunately this method is subject to essentially the same criticism as the moving-film method.

Practically all vectorcardiographers have found it helpful to include the factor of time in their records. This has been achieved by interrupting the electron beam at a known frequency through the application of a fluctuating voltage to the grid or "Z-axis" of the oscilloscope tube. (Again, this technique was first described by Hollmann and Hollmann.[4]) This fluctuating signal can be delivered by an electrical tuning fork or various other types of oscillators. Heretofore this fluctuating voltage has always been used in a symmetrical wave form with the

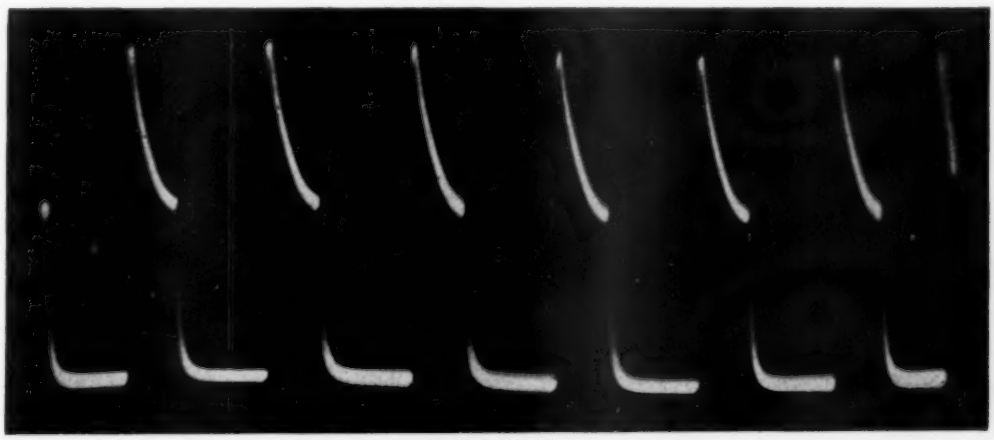

Fig. 1.—A typical wave form of the timing-signal voltage produced by the oscillator described in the text. This wave form was produced at a frequency of 400 cycles per second (peak-to-peak voltage of 30 volts).

result that the first and last parts of any segment of the vectorcardiographic loop isolated by the recurrent extinction of the electron beam have had the same shape. Consequently, the direction of inscription could not be made out. The present report is intended to show how the wave form of the fluctuating voltage can be manipulated so that the direction of inscription of the loop is obvious on first glance at the photographic record of an unharmed, complete, stationary-type vectorcardiographic tracing.

METHOD

The crux of the method lies in the use of what might be called an "imperfect square-wave" oscillator of electron tube type. This oscillator puts out an asymmetrical signal whose shape varies slightly with the frequency selected. A photograph of a typical wave form may be seen in Fig. 1. The circuit diagram of the oscillator may be seen in Fig. 2. This oscillator allows a choice of frequency with

adequate voltage output from about 35 to over 4,000 cycles per second. The peak-to-peak voltage output may be varied from zero to about 120 volts. The whole oscillator, shielded in a grounded metal cabinet, can be made from parts which cost only about $20.00.

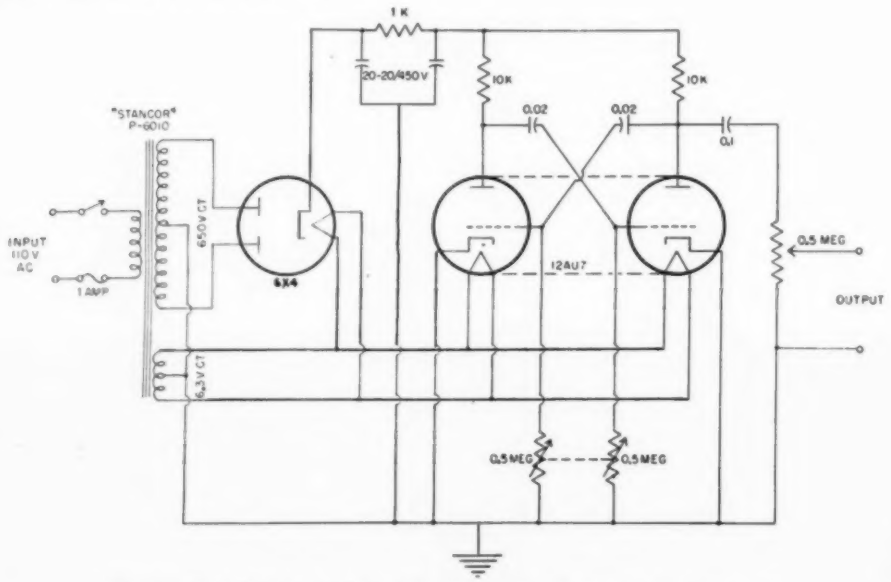

Fig. 2.—The circuit diagram of the oscillator described in the text. All capacities are in microfarads.

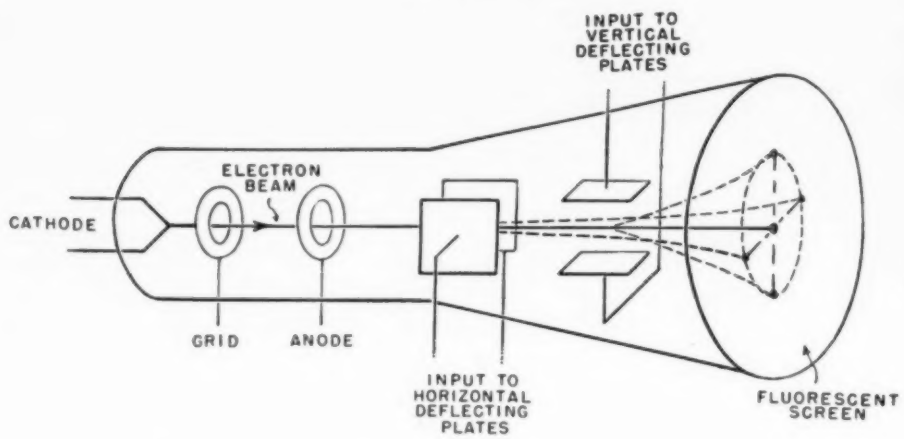

Fig. 3.—A schematic diagram of a cathode-ray oscilloscope tube.

The electron beam of a cathode-ray oscilloscope tube is extinguished when the negative potential applied to the grid drops below a certain figure. (A voltage amplitude of fifteen or more volts is usually required to modulate on the Z-axis of many currently used oscilloscopes.) On the other hand, as the positive potential on the grid is increased, the intensity of the electron beam is increased more or less proportionately. This is reflected on the screen of an oscilloscope tube

by increased brightness and width of the tracing. It is this ability to increase the width of the tracing by changing the grid potential through the use of an asymmetrical timing signal wave which allows us to detect the direction in which the fluorescent spot is being deflected by cardiac potentials. It should be understood that the heart potential is applied only to the deflecting plates and that this circuit is independent of the time signal applied to the grid (Fig. 3).

If one adjusts the voltage output of the oscillator and the beam-intensity control of the oscilloscope so that the sloping part of the oscillator signal will be at the correct voltage to modulate the intensity of the electron beam, then one can produce segmented QRS loops in which each segment will resemble, for example, a comet, a teardrop, or some such fanciful pattern. By minor changes in the setting of the intensity control and/or the oscillator voltage output, one can produce a variety of shapes. However, the setting which produces a comet-shaped segment has been found to be the most satisfactory. Fig. 4 shows the

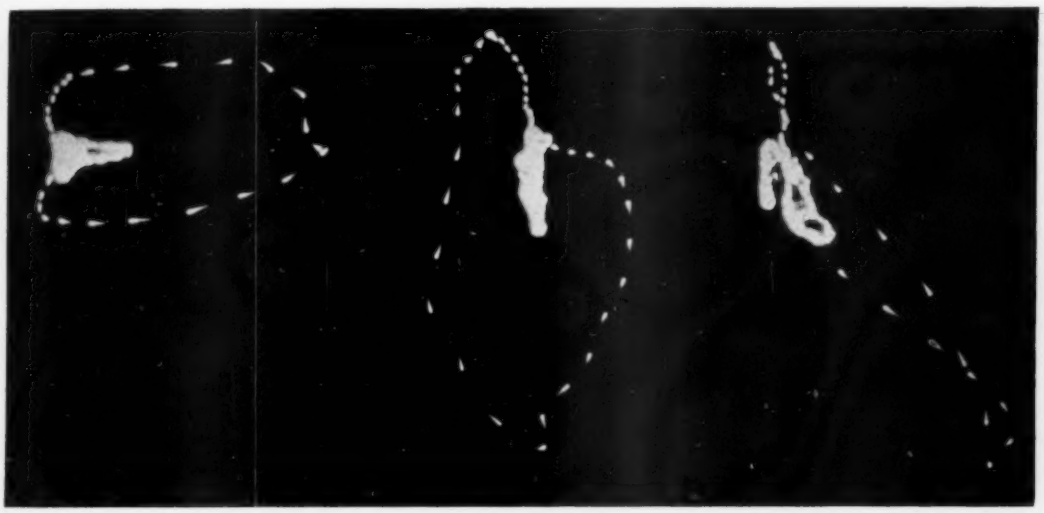

Fig. 4.—A vectorcardiogram of a normal adult showing the direction of rotation of the QRS loops. The lead placement and orientation of the loops is that of Grishman and associates.[2,3] The oscillator frequency was set at 400 cycles per second. The horizontal plane vectorcardiogram is on the left, the sagittal in the center, and the frontal on the right. The tails of the "comets" or tear drops point in the direction of QRS loop rotation—counterclockwise in the horizontal plane, clockwise in the sagittal, and figure-of-eight in the frontal.

vectorcardiogram of a normal adult taken in such a manner. It can be seen that the clockwise or counterclockwise rotation of each loop can be readily recognized, bearing in mind that the direction of inscription was from the head toward the tail of each "comet." By using increased vector amplification and a lower time-signal frequency the same technique may be adapted to the study of P and T loops.

DISCUSSION

The oscillator described above belongs to the square-wave signal group in basic design. The deviations from an ideal square-wave form which it produces are "aberrations" which are characteristic of multivibrators,[6] of which our instru-

ment is one type. It is true that types of asymmetrical signals other than our "imperfect square wave" could be used to produce the same effect. For example, one could use the saw-tooth type of wave that is generated by a conventional thyratron circuit. However, this type of oscillator would not be so versatile. Our instrument can be adjusted so that it gives uniform linear vectorcardiographic segments just like those produced by symmetrical-wave oscillators. It may also be set so that a continuous tracing results, the time and directional factors being indicated by sudden thickening of the line due to rhythmical bursts of suddenly increased and more gradually tapered-off grid potential. This method seems to offer less clarity in the more slowly inscribed parts of the QRS loop without giving significantly more detail elsewhere. (See Fig. 5.) In any event, a considerable saving in time, expense, and effort will result from the use of an asymmetrical time-signal voltage to record directly on the film both the time relationships and the direction of rotation of vectorcardiographic loops.

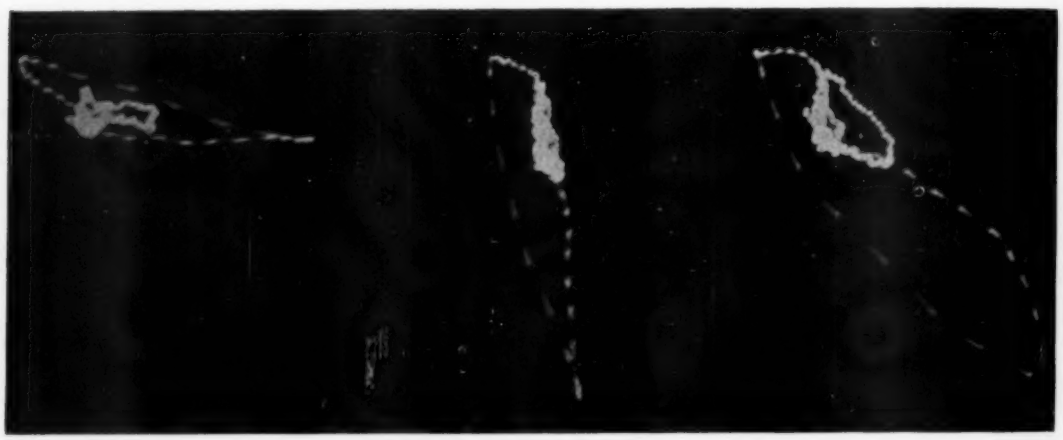

Fig. 5.—A vectorcardiogram of another normal adult, taken in the same manner as that in Fig. 4 except that the oscillator and oscilloscope were set to produce a continuous tracing. The timing and rotation of the QRS loops can still be made out. See text.

SUMMARY

A technique has been described for recording the direction of rotation of vectorcardiographic loops easily and directly through the use of a timing signal of asymmetrical wave form. The advantages of the method and its technical aspects have been discussed briefly.

The author is grateful to Mr. Carter Collins for his help in designing the oscillator.

ADDENDUM

Since submitting this article for publication, it has been noted that the use of an asymmetrical timing signal of saw-tooth pattern has been mentioned in the recent book, *Spatial Vectorcardiography* by A. Grishman and L. Scherlis (Philadelphia, 1952, W. B. Saunders Company).

REFERENCES

1. Bayley, Robert H.: On Certain Applications of Modern Electrocardiographic Theory to the Interpretation of Electrocardiograms Which Indicate Myocardial Disease, AM. HEART J. **26**:769, 1943.
2. Scherlis, L., and Grishman, A.: Spatial Vectorcardiography: Left Bundle Branch Block and Left Ventricular Hypertrophy. II., AM. HEART J. **41**:494, 1951.
3. Grishman, A., Borun, E. R., and Jaffe, H. L.: Spatial Vectorcardiography: Technique for the Simultaneous Recording of the Frontal, Sagittal, and Horizontal Projections. I., AM. HEART J. **41**:483, 1951.
4. Hollmann, W., and Hollmann, H. E.: Neue elektrokardiographische Untersuchungsmethoden. II. Die dreiphasische Vektordarstellung der Potentialresultanten des Herzens, Ztschr. f. Kreislaufforsch. **29**:546, 1937.
5. Chance, B., Hughes, V., MacNichol, E., Sayre, D., and Williams, F.: Waveforms, Vol. 19, p. 171, Massachusetts Institute of Technology Radiation Laboratory Series, New York, 1949, McGraw-Hill Book Company.

THE DEPRESSING EFFECT OF INOSITOL ON SERUM CHOLESTEROL AND LIPID PHOSPHORUS IN HYPERCHOLESTEREMIC MYOCARDIAL INFARCT SURVIVORS

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HERRMANN[1] first reported that choline, methionine, and inositol each depressed serum cholesterol and cholesterol ester levels in hypercholesteremic individuals. In this laboratory, we[2] found lowering of elevated serum cholesterol levels in diabetic patients when inositol was given. Leinwand and Moore[5] also reported that inositol depressed serum lipid levels. Morrison and associates,[4] on the other hand, found that in presumed atherosclerotic individuals given choline values of serum cholesterol rose as frequently as they fell; moreover, the group given choline showed the same type of variation as did a control untreated group who had had myocardial infarcts. Davidson,[3] in his recent critical review of the subject, pointed out the variables inherent in this type of experimentation and came to the conclusion that a definite effect of lipotropic factors on serum lipids remained to be proved.

The present paper reports the apparent effectiveness of inositol in depressing serum cholesterol and lipid phosphorus values in hypercholesteremic subjects with presumed atherosclerosis as evidenced by previous clinically documented myocardial infarcts.

PROCEDURE

Concentrations of serum cholesterol, cholesterol esters[6] and lipid phosphorus[7] were determined on all experimental subjects. All laboratory determinations were performed by one individual. The range of normal for this laboratory for these substances has already been determined.[2]

In the first experiment, twenty-five patients with previous documented myocardial infarcts were selected from the outpatient department of St. Luke's Hospital and the private practice of one of us (J.H.K.). Each patient had survived his most recent infarct by at least six months, and each was free of other disease associated with disturbed lipid metabolism. Two control determinations one to ten days apart were made on the fasting serum of all patients before beginning the experiment. Each subject then began taking 3 Gm. inositol a day

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(two 0.5 Gm. capsules three times daily). Fasting blood samples were drawn at intervals of one, two, four, and eight weeks thereafter. No other change in each patient's therapeutic regimen was started during the course of the experiment. Although it has been shown that drastic dietary restrictions are needed to affect the level of serum cholesterol, each patient was instructed to continue his same dietary habits as before starting the study. No patient reported gastrointestinal intolerance to the medication.

In the second experiment, six additional patients were selected from the outpatient department, using the same criteria as in the first experiment. Each of these patients was given placebo tablets for an eight-week period and similar inositol tablets for the succeeding eight weeks. Fasting blood samples were drawn at frequent intervals throughout the course of the study.

RESULTS

In this series, as in others,[8] average serum lipid values in patients with proved infarcts of the heart were higher than the average of normal persons (Table I). Before inositol, twelve of the thirty-one patients had values above the range of normal of either cholesterol or lipid phosphorus or both. Serum cholesterol esters were proportional in all cases to total cholesterol; lipid phosphorus tended to be high when total cholesterol was high, but the proportion was not as consistent as with cholesterol esters.

In the first experiment, a significant drop in the mean levels of the measured serum lipids occurred during the experimental period (Table I). This decrease in the average is due in large part to a marked drop in the levels of those individuals who were hypercholesteremic at the beginning of the experiment; patients who had control values in the normocholesteremic range experienced for the most part insignificant fluctuations or drops of minor degree. In the hypercholesteremic group, no consistent rate of fall occurred, the values for some patients dropping precipitously over the first week or two, for others falling gradually over longer periods of time. In some cases, marked fluctuations occurred in the values obtained over the eight week period. The percentage change in total serum cholesterol between the control and eight-week values are shown in Fig. 1.

Cholesterol esters fell proportionately to total cholesterol. Lipid phosphorus also tended to fall with decrease in total cholesterol, although to a lesser degree as is shown by the increase in the mean molar ratio of cholesterol to lipid phosphorus over the course of the experiment (Table I).

Three of the hypercholesteremic patients in this group were followed beyond the experiment for periods of time up to one year on inositol. Values for these patients, after the initial drop, stabilized at normal levels with minor fluctuations. One of these patients stopped taking inositol after several months. The lipid values showed a gradual increase, with many fluctuations, but did not return in another three months to his initial hypercholesteremic levels.

The second experiment was undertaken to obtain values over a longer control period so as to observe better the intrinsic individual fluctuations in serum lipid values and thus better to eliminate the effect of chance fluctuations on the results.

TABLE I. VALUES IN mg. % OF SERUM TOTAL CHOLESTEROL AND LIPID PHOSPHORUS IN TWENTY-FIVE MYOCARDIAL INFARCT SURVIVORS BEFORE INOSITOL AND AT INTERVALS OF ONE, TWO, FOUR, AND EIGHT WEEKS ON INOSITOL*

PATIENT	1ST CONTROL		2ND CONTROL		ONE WEEK		TWO WEEKS		FOUR WEEKS		EIGHT WEEKS	
	CHOL. (mg. %)	LIP. P. (mg. %)	CHOL. (mg. %)	LIP. P. (mg. %)	CHOL. (mg. %)	LIP. P. (mg. %)	CHOL. (mg. %)	LIP. P. (mg. %)	CHOL. (mg. %)	LIP. P. (mg. %)	CHOL. (mg. %)	LIP. P. (mg. %)
1.	220	9.3	218	9.3	185	8.9	214	8.4	222	8.4	221	8.2
2.	222	9.3	223	9.3	312	9.7	308	9.7	326	9.6	194	8.1
3.	224	9.4	205	9.1	202	9.1	239	8.7	236	8.7	196	8.4
4.	234	9.4	237	9.4	186	9.0	226	8.4	225	8.5	242	9.3
5.	239	9.0	220	8.7	248	9.2	256	8.4	203	8.2	204	8.2
6.	239	9.6	239	9.6	193	8.2	235	8.6	255	8.3	217	8.0
7.	256	9.6	260	9.6	193	8.1	192	8.2	229	8.5	220	8.2
8.	259	9.6	254	9.6	—	—	—	—	239	9.5	239	9.5
9.	265	9.6	266	9.6	242	9.1	269	9.3	280	9.0	186	8.0
10.	265	9.4	263	9.4	271	9.3	236	8.6	239	8.7	209	8.1
11.	274	9.7	268	9.7	236	8.4	240	9.4	278	8.9	195	8.1
12.	291	9.8	284	9.8	219	8.8	226	8.5	197	8.2	197	8.1
13.	291	10.4	292	10.5	282	10.4	274	10.3	239	10.0	246	9.5
14	296	—	294	10.2	275	10.0	274	—	265	9.3	239	9.1
Mean	255	9.5	252	9.6	234	9.0	245	8.9	245	8.8	215	8.5
15.	310	9.7	308	9.7	287	9.3	325	9.6	226	8.6	190	8.2
16.	332	10.0	338	10.1	231	8.6	212	8.3	211	8.2	200	8.1
17.	333	10.7	339	10.7	280	9.3	269	9.2	265	8.6	211	8.3
18.	342	10.3	342	10.3	337	10.3	282	10.0	278	9.9	256	9.7
19.	342	11.3	342	11.2	233	8.9	239	8.9	217	8.3	200	8.1
20.	389	—	389	—	367	10.3	318	10.0	299	9.8	326	10.3
21.	395	11.2	396	11.3	232	8.6	209	8.4	196	8.2	180	8.4
22.	402	11.4	410	11.3	360	11.0	320	10.7	300	10.4	220	9.5
23.	489	—	486	—	462	—	436	12.5	410	11.6	274	10.2
24.	500	12.5	496	12.5	201	8.4	248	9.4	231	8.6	192	8.0
25.	598	14.7	598	14.7	564	14.4	547	14.1	496	12.5	432	11.1
Mean	403	11.3	404	11.4	323	9.9	309	10.1	284	9.5	244	9.1
Mean and Range (for entire group)	320 (220–598)	10.2 (9.3–14.7)	318 (205–598)	10.2 (8.7–14.7)	275 (185–564)	9.4 (8.1–14.4)	275 (192–547)	9.5 (8.2–14.1)	263 (197–496)	9.1 (8.2–12.5)	227 (186–432)	8.7 (8.0–11.1)

*The first 14 lines represent patients whose control values lie within the range of normal for this laboratory, the remaining of those above the range of normal. The mean and range of normal as previously determined[2] in this laboratory are: Total cholesterol 236 (188 to 297). Lipid phosphorus 9.3 (8.8 to 10.2). Values for serum cholesterol esters, which varied only within the range of 68 to 74 per cent of total cholesterol throughout, are omitted.

normal. The mean and range of normal as previously determined in this laboratory are: Total cholesterol 256 (188 to 297). Lipid phosphorus 9.8 (8.8 to 10.2). Values for serum cholesterol esters, which varied only within the range of 68 to 74 per cent of total cholesterol throughout, are omitted.

TABLE II. VALUES IN MG. % FOR TOTAL CHOLESTEROL, CHOLESTEROL ESTERS, AND LIPID PHOSPHORUS IN SIX MYOCARDIAL INFARCT SURVIVORS GIVEN PLACEBOS AND LATER INOSITOL*

	PLACEBO					INOSITOL				
1.		(7) 171/126 8.8	(4) 188/137 8.9	(2) 222/156 9.2	215/148 9.1	(3) 180/136 8.9	(7) 276/194 9.6	(9) 259/179 9.5	(14) 247/170 9.4	
2.	(8) 256/176 11.6	(7) 297/199 10.7	(5) 282/204	(2) 267/194 9.4	295/218	(2) 266/184 9.5	(4) 266/183 9.7	(6) 280/196 10.0	(8) 261/180 9.5	
3.	(7) 269/195 9.2	(6) 239/167 9.0	(4) 250/172 9.2	(2) 246/173 9.0	312/217 15.0	(2) 272/190 9.9	(4) 223/160 9.2	(6) 274/191 9.9	(8) 246/173 9.4	(10) 230/163 9.3
4.		(6) 280/207 9.3	(5) 235/155 9.2	(2) 308/227 14.5	289/200 9.2	(2) 224/161 9.0	(4) 222/160 9.1	(6) 260/180 9.7	(8) 250/174 9.4	(10) 232/162 9.3
5.	(7) 298/199 10.6	(6) 239/168 9.1	(4) 274/200 9.3	(2) 231/178 9.1	297/207 11.6	(4) 244/180 9.4	(6) 257/178 9.4	(8) 250/178 9.4	(10) 236/166 9.2	
6.		(7) 300/236 14.8	(6) 359/252 15.6	(1) 273/189 9.4	333/240 14.0	(2) 323/237 12.2	(4) 298/200 11.0	(6) 270/185 10.6	(8) 237/166 9.3	(10) 240/166 9.4

*Figures in parentheses before the values indicate the number of weeks before or after inositol was begun.

The values for these patients are shown in Table II. The only one of these patients who happened to have consistently elevated control values showed a marked drop while on inositol. Another patient, whose control values were consistently at the lower end of the normal range, showed a moderate increase in his values over the inositol period. The remaining four patients, who had control values in the normal range, showed slight to moderate drops when the average for the control period was compared with the average for the inositol period. However, marked fluctuations over the entire experimental period were observed, with values during the inositol period being in some cases higher than any observed during the control period.

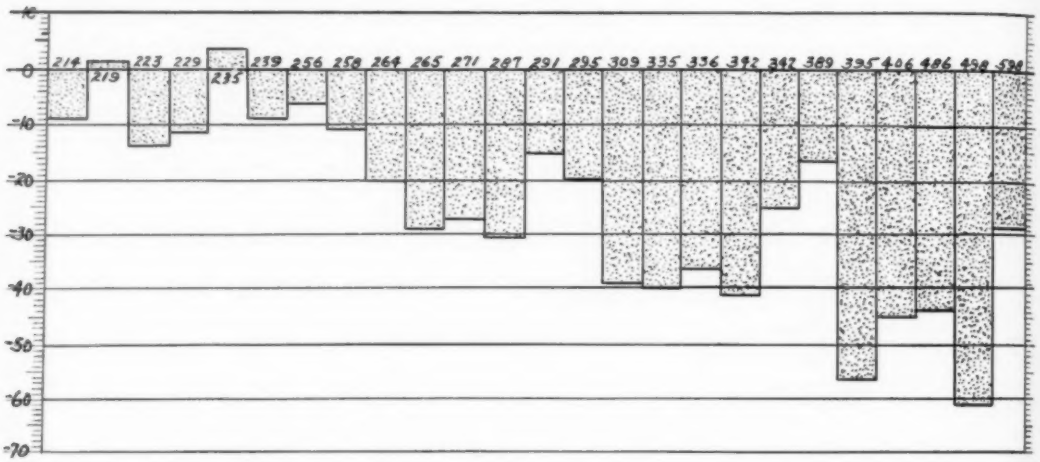

Fig. 1.—Percentage change in total cholesterol of twenty-five myocardial infarct survivors when the values after eight weeks on inositol are compared with the average of two control values.

COMMENT

Two major questions are raised by the data presented above. The first concerns the question of whether or not inositol actually depresses serum cholesterol levels. It is well known that there is considerable technical difficulty inherent in serum lipid determinations. Moreover, it is also known[9] that there is a variation of as much as 15 per cent in individual cholesterol levels when frequent determinations are made on the fasting serum of normal individuals over the course of a year. In presumed atherosclerotic individuals, there is evidence[10] that these fluctuations are of even greater degree; this is borne out by the fluctuations observed in the individuals in whom more frequent control values were obtained. For these reasons, some of the changes noted above may not be significant, especially the inconsistent fluctuations noted in the normocholesteremic patients. In those patients who had hypercholesteremic control values, however, there is every reason to believe that the changes observed can be attributed to inositol, since these changes were so large and of such uniform direction.

The second question concerns the significance of the above findings in relation to the general problem of the therapy and prevention of atherosclerosis.

While it would appear empirically to be of value to lower serum lipid levels in atherosclerotic patients, it has not been proved, and it is not the contention of this paper that this would prevent or cure the pathologic process. As Davidson has pointed out, there is conflicting evidence that lipotropic factors are of value in the experimental animal or in clinical atherosclerosis. It will require long-term well-controlled studies with large numbers of subjects to give the final answer as to the usefulness of lipotropic factors in human atherosclerosis.

SUMMARY

1. Twelve of thirty-one unselected survivors of myocardial infarction had fasting values for serum cholesterol and/or lipid phosphorus above the range of normal.

2. With the administration of inositol for an eight-week period, a fall occurred in the mean level of the measured serum lipids.

3. The most significant drop occurred in those individuals who had control values in the hypercholesteremic range.

REFERENCES

1. Herrmann, G. R.: Some Experimental Studies in Hypercholesteremic States, Exper. Med. & Surg. **5**:149, 1947.
2. Felch, W. C., and Dotti, L. B.: Depressing Effect of Inositol on Serum Cholesterol and Lipid Phosphorus in Diabetics, Proc. Soc. Exper. Biol. & Med. **72**:376, 1949.
3. Leinwand, I., and Moore, D. H.: Simultaneous Studies on the Serum Lipids and the Electrophoretic Pattern of the Serum Protein in Man: (1) Action of Inositol and Other Substances, AM. HEART J. **38**:467, 1949.
4. Morrison, L. M., Gonzales, W. F., and Hall, L.: The Significance of Cholesterol Variations in Human Blood Serum, J. Lab. & Clin. Med. **34**:1473, 1949.
5. Davidson, J. D.: Diet and Lipotropic Agents in Arteriosclerosis, Am. J. Med. **11**:736, 1951.
6. Sperry, W. M., and Brand, F. C.: The Colorimetric Determination of Cholesterol, J. Biol. Chem. **150**:315, 1943.
7. Youngburg, G. E., and Youngburg, M. V.: Phosphorus Metabolism: I. A System of Blood Phosphorus Analysis, J. Lab. & Clin. Med. **16**:158, 1930.
8. (a) Morrison, L. M., Hall, L., and Chaney, A. L.: Cholesterol Metabolism: Blood Serum Cholesterol and Ester Levels in 200 Cases of Acute Coronary Thrombosis, Am. J. M. Sc. **216**:32, 1948.
   (b) Lerman, J., and White, P. D.: Metabolic Changes in Young People With Coronary Heart Disease, J. Clin. Investigation **25**:914, 1946.
   (c) Gertler, M. M., Garn, S. M., and Bland, E. F.: Age, Serum Cholesterol and Coronary Artery Disease, Circulation **2**:517, 1950.
9. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry Interpretations, Vol. I, ed. 2, Baltimore, 1946, Williams & Wilkins Company, p. 470.
10. Steiner, A., and Domanski, B.: Serum Cholesterol Levels in Coronary Atherosclerosis, Arch. Int. Med. **71**:397, 1943.

MEPHENTERMINE—AN EFFECTIVE PRESSOR AMINE

Clinical and Laboratory Observations

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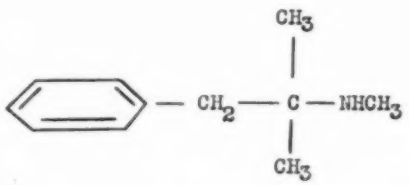
MEPHENTERMINE* (N-methylphenyl tertiary butylamine), a new synthetic pressor substance,[1] chemically resembles many of the commonly used sympathomimetic amines such as amphetamine and desoxyephedrine. It differs from all other clinically used pressor amines in that the amino group is attached to a tertiary carbon atom. It has the following formula:



Since it contains no asymmetric carbon atom it has no *d* and *l* forms. Mephentermine differs from amphetamine and desoxyephedrine in that it is one-half as toxic (as measured by the LD_{50} dose in white mice) and its cerebral stimulation is only one-fourth as great.[1] When given orally to medical students in doses as high as 60 mg. per day there were no cerebral effects. There was no anorexigenic effect in human beings receiving 10 mg. tablets three times daily.[1] Pharmacologic studies on dogs[1] have shown that both qualitatively and quantitatively mephentermine resembles ephedrine as to intensity and duration of pressor activity. Like the other synthetic pressor amines, injections repeated at too frequent intervals result in decreased response (tachyphylaxis).

In anticipation of the use in certain hypotensive states of a pressor substance having little demonstrable effect on myocardial irritability, physiologic studies were carried out in dogs and selected human beings.

ANIMAL EXPERIMENTS

Methods.—Preliminary experiments were performed in anesthetized dogs receiving doses equivalent to those used in human beings (0.3 to 0.5 mg./kg.). Femoral arterial blood pressure was recorded by means of a Hamilton manometer

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*Marketed as Wyamine (Wyeth Incorporated, Philadelphia, Pa.). The drug used in this study was kindly supplied by Dr. Joseph Seifter, Wyeth Institute of Applied Biochemistry.

or Sanborn electromanometer. Cardiac output was determined in the intact animal using the Fick principle, mixed venous blood being obtained from the right ventricle by means of a cardiac catheter. Right ventricular and pulmonary artery pressures were also obtained via the cardiac catheter. Coronary blood flow was recorded in open-chest preparations by means of a rotameter inserted into the left coronary artery,* under constant perfusion pressure. Oxygen consumption was measured by means of a Sanborn metabulator connected to an intratracheal catheter.

After a control period, mephentermine was administered by intravenous infusion until a rise in mean blood pressure of 10 to 30 per cent above control level was maintained. Usually approximately 0.3 to 0.5 mg./kg. over a six to ten minute period had the desired effect.

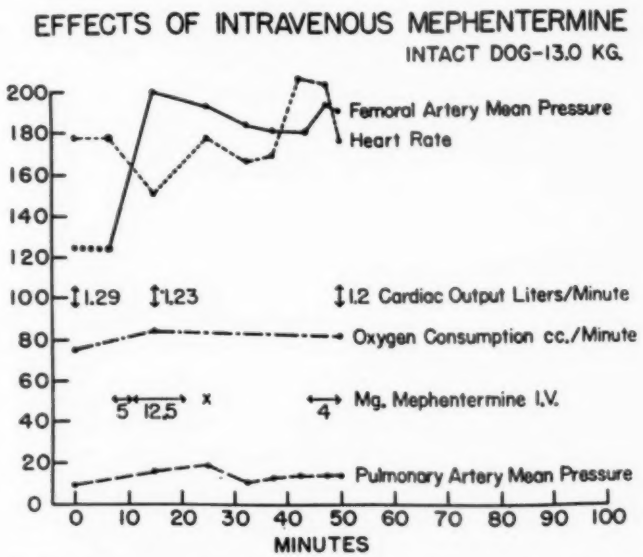

Fig. 1.—Effects of mephentermine on the circulation of a normal dog. Thirteen kilogram dog anesthetized with phenobarbital. Closed chest preparation. Cardiac catheter inserted through jugular vein into pulmonary artery. Mephentermine administered by slow intravenous infusion at rates indicated on graph. At point X, following rapid administration of an excessive dose of mephentermine, frequent premature ventricular systoles occurred. These ceased following discontinuance of the drug and did not reappear with subsequent smaller doses. (Discussed in text.)

Results.—By regulating the rate of administration of the drug the desired pressor response could be achieved easily. Associated with this pressor response there was usually little change in the heart rate except for reflex slowing. Pulmonary artery pressure increased slightly. There were no significant electrocardiographic effects. Oxygen consumption was slightly increased and there was a variable but definite increase in the respiratory rate. Cardiac output at the height of the pressor effect showed no significant variation from control values.

Fig. 1 illustrates a typical pressor response in an intact dog. In this experiment the rapid infusion of 5 mg. of mephentermine produced a marked pressor response which was maintained at an excessive level by a continuous infusion of

*We are indebted to Dr. John Chambliss for assistance in these experiments.

12.5 mg. The mean blood pressure rose from 125 mm. Hg to 200, at which time there was slowing of the heart rate from 178 per minute to 150, later there was an acceleration to 200. The cardiac output was essentially unchanged (1.29 L./min. to 1.23); oxygen consumption increased from 75 c.c./min. to 82; mean pulmonary artery pressure rose from 10 mm. Hg to 16. Forty-five minutes after the start of infusion (total, 21.5 mg.), the cardiac output was still unchanged.

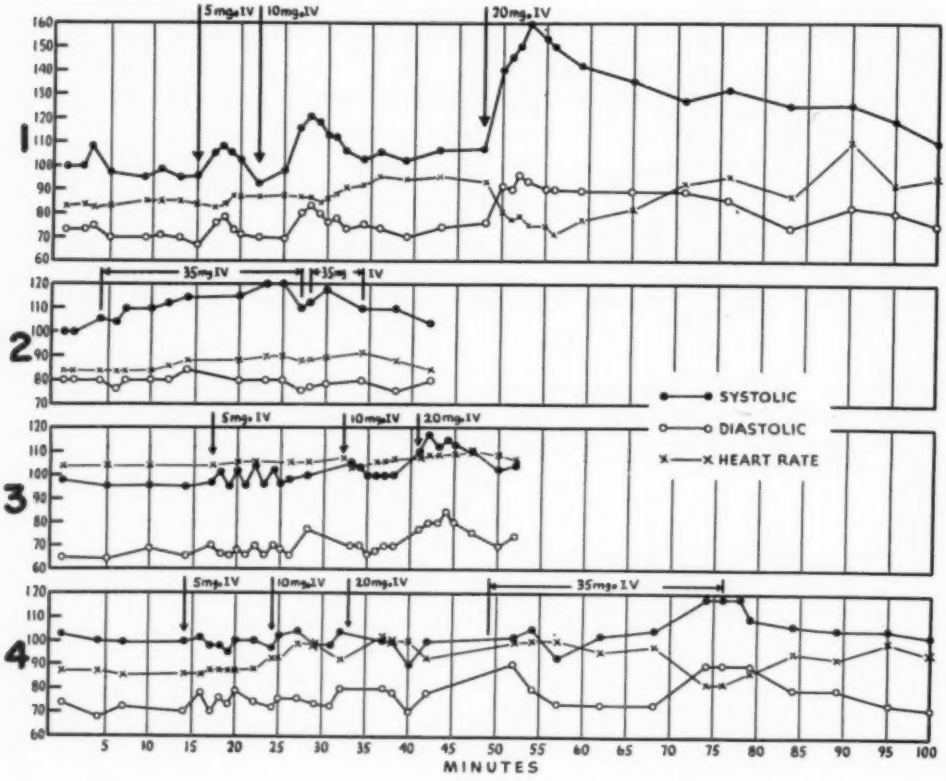

Fig. 2.—Response of relatively hypotensive patients to intravenous mephentermine.
Case 1, a 45-year-old Negro woman, with tabes dorsalis and sarcoidosis.
Case 2, a 73-year-old white man, with malignant melanoma and generalized metastases.
Case 3, a 33-year-old Negro woman, with sclerodermal heart disease, prior to treatment.
Case 4, a 33-year-old Negro man, with tuberculous pericarditis. (Discussion in text.)

In open-chest preparations, despite the maintenance of constant coronary artery perfusion pressure, coronary blood flow was increased significantly. The increase in coronary flow bore no direct relationship to the degree of pressor response.* Excessively large doses of the drug produced tachycardia, premature ventricular beats, and elevation in the pulmonary as well as systemic blood pressure. These effects disappeared when the pressor effect subsided.

*A more detailed study is being made by Dr. R. W. Eckstein and associates.

PRELIMINARY OBSERVATIONS ON HUMAN BEINGS

Methods.—Mephentermine was administered to selected volunteer patients in the following categories: (1) hypotensive (usually persons with chronic illnesses) 9 patients, (Fig. 2); (2) normotensive, 6 patients, (Fig. 3); (3) hypertensive, 5 patients, (Fig. 4). With these patients in a basal state, a slow intravenous infusion of 5 per cent glucose in water was maintained throughout the period of observation. Intravenous doses of the drug were given through a three-way stopcock, the patient being unaware of the time of administration of the drug.

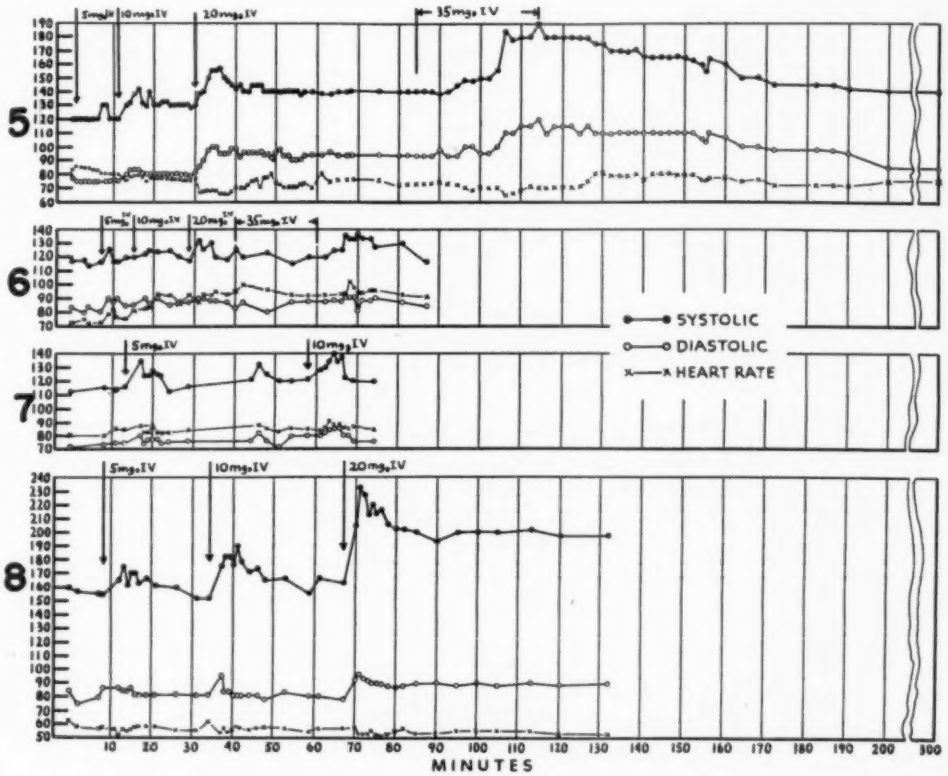

Fig. 3.—Response of normotensive patients to intravenous mephentermine.
Case 5, a 34-year-old Negro man, with central nervous system syphilis.
Case 6, a 41-year-old white man, convalescent pneumonia.
Case 7, a 64-year-old white man, with osteoarthritis of the spine.
Case 8, a 73-year-old white man, with peptic ulcer. (Discussion in text.)

The following observations were made during a control period and following administration of the drug: arterial blood pressure by means of the conventional cuff and mercury manometer (in some cases femoral arterial pressure was recorded by a Sanborn electromanometer), electrocardiogram, heart rate, respiratory rate and volume, and cerebral and pupillary changes. The drug was administered in graded doses of 5 mg., 10 mg., and 20 mg. and observations recorded until blood pressure returned to control levels. Preliminary studies had shown that less than 5 mg. produced an insignificant pressor effect. Most patients also received a slow intravenous infusion of 35 mg. over a one-half hour period. The total volume of infusions did not exceed 50 c.c.

In four additional patients cardiac output was determined by the Fick principle, using right heart catheterization (Fig. 5). Arterial samples were obtained from the femoral artery, and oxygen consumption was determined by means of a Sanborn metabulator. Following a control period, the drug was administered slowly intravenously until the desired pressor effect was obtained, at which time determinations of cardiac output were again made.

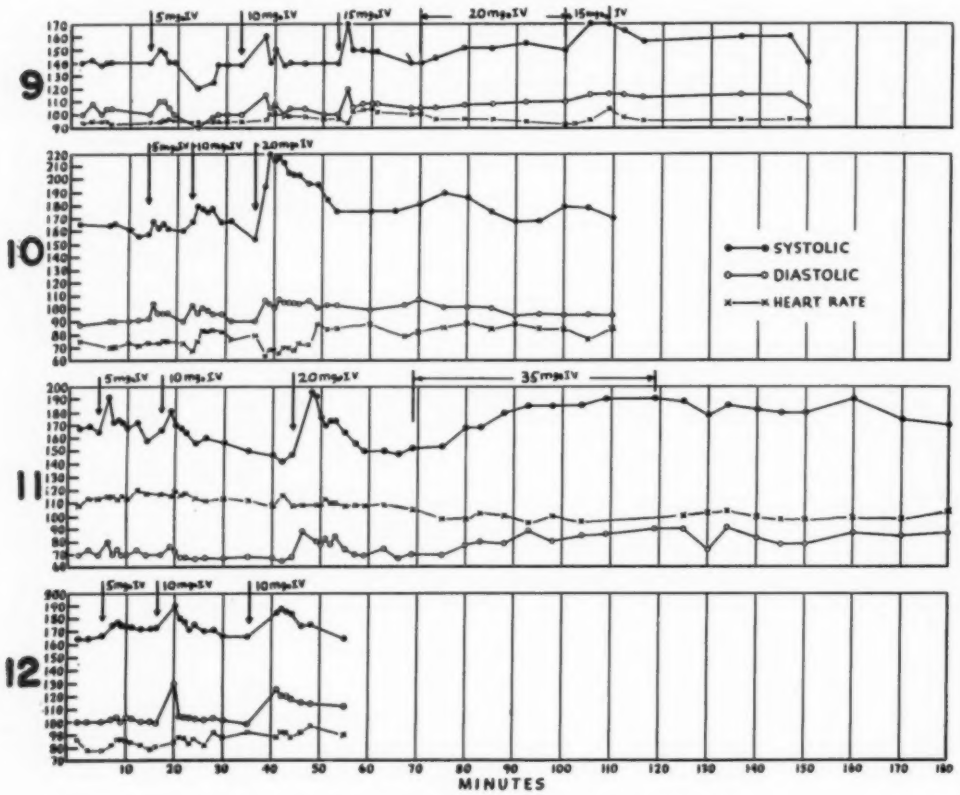

Fig. 4.—Response of hypertensive patients to intravenous mephentermine.
Case 9, a 60-year-old white man, with tabes dorsalis and hypertension.
Case 10, a 55-year-old white woman, with mild diabetes and hypertension.
Case 11, a 59-year-old white woman, with generalized arteriosclerosis and systolic hypertension.
Case 12, a 62-year-old white man, with mild hypertension. (Discussion in test.)

Results.—Figs. 2 to 5 demonstrate graphically the effects of mephentermine on representative control patients. Following a single intravenous injection an immediate pressor effect is obtained, the magnitude and duration of which in an individual patient is related to the dose (Fig. 2, Cases 1 and 3; Fig. 3, Cases 5 and 8; Fig. 4, Cases 10 to 12). In Case 1, 5 mg. produced a rise of 10 mg. Hg systolic and diastolic pressures which subsided in seven minutes; 10 mg. produced approximately twice as great an effect which did not completely subside in twenty minutes; 20 mg. elevated the blood pressure from 108/74 to 160/98 associated with a reflex slowing of the heart rate from 92 per minute to 74. The blood pressure did not return to control levels after fifty minutes, an unusually prolonged response. In most cases the return to control levels was more rapid.

There were individual variations in response to the drug. For example, in Cases 4, 6, 7, 8, and 9, doses which were effective in most cases produced little effect. In general, patients with chronic wasting disease showed a less striking response.

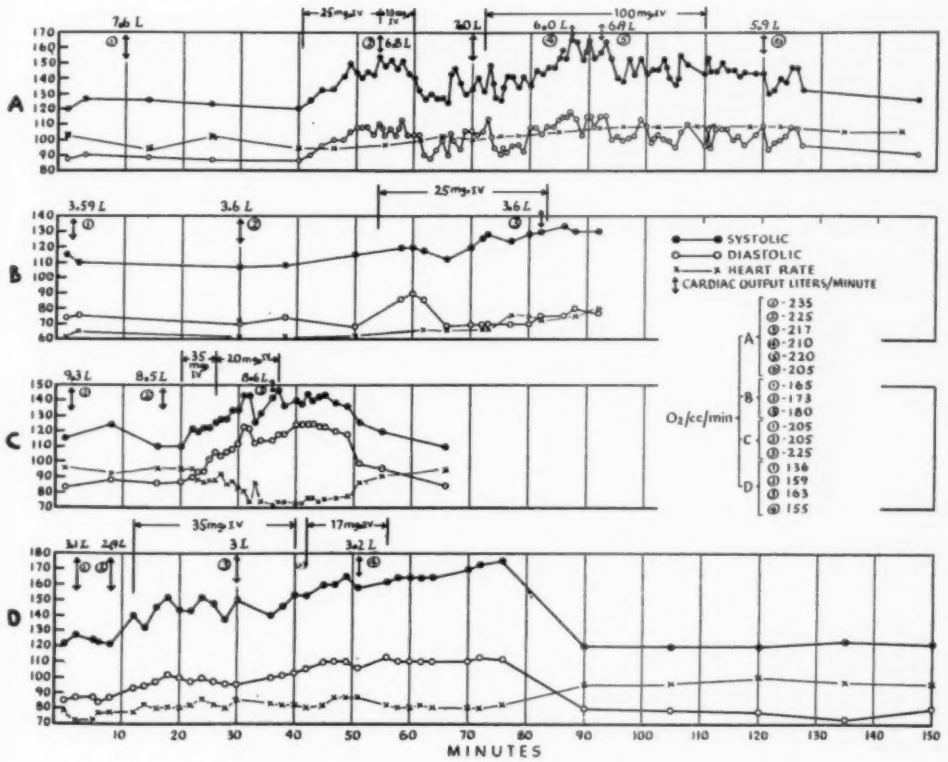

Fig. 5.—Effect of mephentermine on the circulatory dynamics of four patients, as studied by cardiac catheterization.

A, Case 13, a 47-year-old white woman, with cirrhosis of the liver.

B, Case 14, an 82-year-old white man, studied on the thirtieth day following acute myocardial infarction.

C, Case 15, a 33-year-old Negro woman, following treatment with ACTH. Same patient as Case 3 in Fig. 2.

D, Case 16, a 68-year-old white man, with arteriosclerotic heart disease and remote cerebral thrombosis. In the above cases, a significant pressor response was obtained without altering the cardiac output or mechanism. (Discussion in test.).

A more sustained elevation could be obtained by a continuous intravenous infusion (Cases 2, 5, 11, 13 to 16). In fifteen additional control patients intramuscular or subcutaneous* injections of 10 to 35 mg. produced a slower but more sustained (one to four hours) response. There was no evidence of local tissue reaction.

*The addition of 75 turbidity reducing units of hyaluronidase (Wydase, Wyeth Incorporated) to the subcutaneous dose of mephentermine facilitated absorption.

In the four cases in which cardiac output was determined by right heart catheterization a good pressor response was maintained by continuous intravenous infusion of mephentermine (Fig. 5). In Case 13, (Fig. 5,*A*) following the infusion of 25 mg. in 13 minutes, the blood pressure had risen from a control level of 120/85 mm. Hg to 150/110 with a slight decrease in heart rate. The cardiac output showed an insignificant decrease from 7.6 to 6.8 liters per minute. Ten minutes after the cessation of infusion of 35 mg., the blood pressure had fallen to 130/100 and the cardiac output was 7.0 L./min. The infusion of 50 mg. raised the blood pressure to 165/115 and successive cardiac outputs were 6.0 and 6.9 L./min. Ten minutes after cessation of 100 mg. infusion the blood pressure was 140/110 and cardiac output was 5.9 L./min. There was little variation of the pulse rate throughout. Pulmonary artery pressure remained relatively constant except for a slight rise (25/8 to 30/10) during the height of the pressor response. Oxygen consumption varied slightly with the changes in cardiac output.

In the case of an 82-year-old man on the thirtieth day following acute myocardial infarction (Fig. 5,*B*), control cardiac outputs were 3.59 and 3.60 L./min., such low values usually being found in these patients.[2] The blood pressure was 110/75 mm. Hg. Infusion of 25 mg. of mephentermine raised the blood pressure to 130/80 with no change in cardiac output. There was an increase of heart rate from 60 to 75 per minute.

In the case of a 33-year-old woman treated with ACTH for scleroderma (Fig. 5,*C*), a sustained pressor response was obtained with an infusion of 55 mg. in 18 minutes, the blood pressure rising from 110/85 to 145/120 as the heart rate decreased from 95 to 75 per minute. The control cardiac outputs were 9.3 and 8.6 L./min. At the height of the pressor response the cardiac output was 8.6 L./min.

In the case of a 66-year-old man with arteriosclerotic heart disease and mild failure (Fig. 5,*D*), the administration of 35 mg. raised the blood pressure from 120/85 to 150/98 with a slight increase in heart rate. During the control period the cardiac output was 3.1 and 2.9 L./min. and at the height of pressor response, 3.0 L./min. The subsequent infusion of 17 mg. raised the blood pressure to 160/110 but the cardiac output was maintained at 3.2 L./min.

In general, intracardiac pressures were unaltered although there was usually a slight elevation of pulmonary artery pressure associated with a significant pressor response. Oxygen consumption remained relatively constant although respiratory rate was slightly increased. Cardiac output was unaffected despite significant elevation of blood pressure.

The heart rate usually was not significantly altered by the drug, although occasionally there was rather marked vagal slowing associated with a good pressor response (Cases 1, 5, 10, 15). In no case did serial electrocardiograms show significant changes. No ectopic beats or arrhythmias were produced.

Evidence of cerebral stimulation or other side effects were not observed except in one patient (Case 4), who began to perspire profusely near the termination of his study. Pupillary changes were transient. Blood glucose levels were unaltered.

DISCUSSION

Innumerable compounds with so-called sympathomimetic activity have been described and studied since Barger and Dale[3] defined the basic structural requirements for pharmacologic activity and introduced the term "sympathomimetic" in describing their mode of action. The relationship between pharmacologic action and chemical constitution and configuration of the optical isomers of ephedrine and related compounds was illustrated by Chen and associates[4] and led to more basic understanding of sympathomimetic amines. Further work by Tainter[5] extended this understanding. In general, it may be said that the responses produced by these drugs are those produced by stimulation of adrenergic nerves.[5] Depending upon variation in structure, the intensity and localization of response to these amines vary greatly.

The desirability of a drug with a primary pressor effect with little or no "direct" myocardial stimulation has long been recognized. Ephedrine,[6] amphetamine,[7] Neosynephrine, and Propadrine,[4] Paredrine,[8] desoxyephedrine, and various others have been utilized for primary pressor action, but all have some direct action upon the myocardium.

The recognition of norepinephrine,[9] its demonstration in the adrenal medulla,[10] and its distinct mode of action as compared to epinephrine[11] has further aided in predictability of pressor response. Although norepinephrine is an overall vasoconstrictor,[12] it presumably also has a direct myocardial effect.[13]

Mephentermine is structurally different from all other clinically used amines. However, it appears to possess a distinct pressor action. Clinically, we have demonstrated a definite immediate pressor response to adequate doses. In the doses employed there was little direct myocardial effect, as measured by the usual pharmacologic methods, that is, change in rate, rhythm, and irritability. Thus mephentermine has a hypothetical norepinephrine-like action. In general, there was slowing of the heart rate associated with pressor action, indicating reflex vagal stimulation. However, the determination of inotropic effect depends upon investigation of its effect on the isolated myocardium. The return of blood pressure to control levels was usually rapid after withdrawal of the drug indicating rapid excretion or inactivation. Occasionally there was a prolonged response. Significantly, there was a proportional rise of the systolic and diastolic pressures. The rise in diastolic pressure is desirable for increasing coronary flow.

Despite a significant increase in peripheral resistance, cardiac output was not significantly altered. Thus, the work of the heart was increased.[14] An elevation of mean blood pressure from 100 to 120 mm. Hg represented approximately a 20 per cent increase in the work of the heart. The increased peripheral resistance may result in temporarily increased diastolic volume of the left ventricle[14] which increased the strength of discharge. The increase in cardiac work thus is not necessarily evidence of inotropic effect of the drug.

Ephedrine and epinephrine have been shown to increase cardiac work by increasing the cardiac output and peripheral resistance,[15] while Benzedrine and Paredrine do not increase the cardiac output in producing a pressor response.[16] Likewise norepinephrine produces no significant alteration of cardiac output.

Since most hypotensive states have an element of vasodilatation which can be overcome,[11] a primary vasopressor action is desirable. The use of norepinephrine in shock associated with myocardial infarction has been recently suggested,[17] although the danger of its use in the presence of inadequate coronary circulation has been pointed out.[18]

The demonstration of an increase in coronary artery flow independent of changes in aortic pressure following administration of mephentermine requires further investigation. Clinically the elevation of systolic blood pressure and coronary flow appear to be desirable features of this drug, especially in the treatment of hypotension accompanying myocardial infarction,[13] and of hypotensive states in patients with coronary insufficiency.

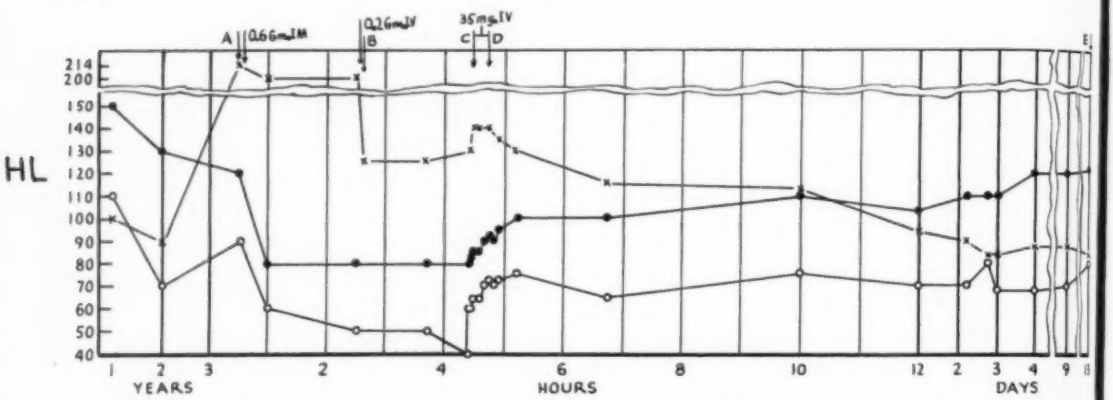

Fig. 6.—Effect of mephentermine on the hypotensive state following conversion of ventricular tachycardia. A 54-year-old white man with a history of two previous myocardial infarcts was admitted (*A*) because of a ventricular tachycardia (rate 214 per minute). Thirty minutes after admission, 0.6 Gm. of intermuscular quinidine lactate was ineffective. The blood pressure fell to 80/60 mm. Hg. Two and one-half hours after admission, 0.2 Gm. of intravenous quinidine (*B*) converted the mechanism to sinus tachycardia, with a rate of 120. However, the blood pressure remained at shock levels (*C*). Mephentermine (35 mg.) was administered intravenously and produced a prompt pressor response which was associated with marked clinical improvement (*D*). The blood pressure rose to 110/76 mm. Hg and was maintained until the patient's discharge on the thirteenth hospital day (*E*).

TREATMENT OF HYPOTENSIVE STATES

The preliminary observations on dog and man, therefore, demonstrated that mephentermine in the doses employed produced a significant pressor response without undesirable side effects. The use of this drug was extended to the treatment of more than 100 patients with acute hypotension due to various causes. Included in this series were twenty-one cases of myocardial infarction with shock which will be reported subsequently.[19]

Mephentermine was administered to fifty patients with hypotension occurring during operation.* In forty cases undergoing cardiac operations (mitral commissurotomy, Beck coronary sinus-aorta graft,[20] Potts or Blalock operations), intravenous doses of 10 to 35 mg. produced prompt restoration of blood pressure from hypotensive levels without initiating arrhythmias. In three cases of surgical shock associated with hemorrhage, mephentermine produced a sustained pressor response although whole blood transfusion alone had failed.[19]

*Mephentermine is also valuable in controlling the hypotension in spinal anesthesia.[21]

Mephentermine elevated the blood pressure effectively in five miscellaneous cases of marked hypotension of medical etiology (after conversion of ventricular tachycardia, aortic stenosis with congestive failure, pulmonary infarction). In Fig. 6, the course of events is presented in a patient with shock following ventricular tachycardia. The restoration of blood pressure without the production of ectopic rhythms is noteworthy in view of the advanced coronary disease and recent tachycardia in this case.

In eight obviously terminal and moribund cases, little or no pressor response was elicited by mephentermine (or other pressor drugs).

DOSAGE

On the basis of the above experiences, the following recommendations are made for the use of mephentermine as a pressor drug. A practical dosage schedule consists of an intravenous priming dose of 10 to 20 mg. or more, followed by an intravenous infusion of approximately 1 mg. per minute. The rate of intravenous infusion can be regulated to obtain the desired blood pressure. A sustained pressor response can be obtained by intramuscular injection of 15 to 35 mg. at one-half hour intervals, or longer.

SUMMARY

1. Mephentermine (Wyamine) a new pressor substance with theoretical norepinephrine-like activity has been shown to produce a rapid predictable pressor response in volunteer human beings (controls) and dogs.

2. With the doses employed, there was little or no direct action upon the heart as measured by changes in rate, rhythm, and irritability.

3. Side reactions such as cerebral stimulation, pupillary changes, blood sugar changes, respiratory stimulation, and metabolic rate increase were absent or insignificant.

4. The cardiac output was relatively unaltered and heart work was increased in normal and hypotensive patients. Coronary flow in dogs was increased even under constant coronary perfusion pressure.

5. Mephentermine appears to be a suitable drug for use in treating acute hypotensive states, especially shock following myocardial infarction. It has proved effective in sustaining blood pressure in cardiovascular operations without producing arrhythmias.

REFERENCES

1. Seifter, J., Eckfeld, D. K., and Abell, L. L.: Pharmacology of N-Methyl-ω-Phenyl-Tert-Butylamine, Abstracts of Division of Medicinal Chemistry, American Chemical Society, Sept., 1949.
2. Pritchard, W. H., Hellerstein, H. K., and Brofman, B. L.: Cardiac Output Following Acute Myocardial Infarction. To be published.
3. Barger, G., and Dale, H. H.: Chemical Structure and Sympathomimetic Action of Amines, J. Physiol. **4**:19, 1910.
4. Chen, K. K., Wu, C. K., and Henriksen, E.: Relationship Between Pharmacological Action and Chemical Constitution and Configuration of the Optical Isomers of Ephedrine and Related Compounds, J. Pharmacol. & Exper. Therap. **36**:363, 1929.

5. Tainter, M. L.: Comparative Actions of Sympathomimetic Compounds: Phenyl and Substituted Phenyl Derivatives, Non Phenylic Ring Compounds and Aliphalic Amines, Arch, internat. pharmacodyn. **46**:192, 1933.
6. Chen, K. K., and Schmidt, C. F.: The Action of Ephedrine, the Active Principle of the Chinese Drug Ma Huang, J. Pharmacol. & Exper. Therap. **24**:339, 1924.
7. Piness, G., Miller, H., and Alles, G. A.: Clinical Observations on Phenylaminoethanol Sulfate, J. A. M. A. **94**:790, 1940.
8. Alles, G. A.: The Comparative Physiological Actions of D1-β-phenyl-isopropylamines. 1. Pressor Effect and Toxicity, J. Pharmacol. & Exper. Therap. **48**:161, 1933.
9. von Euler, U. S.: A Specific Sympathomimetic Ergone in Adrenergic Nerve Fibers (Sympathin) and its Relations to Adrenaline and Nor-Adrenaline, Arch. physiol. Scandinav. **12**:73, 1946.
10. Goldenberg, M., Faber, M., Alston, E. J., and Chargaff, E. C.: Evidence for Occurrence of Nor-epinephrine in the Adrenal Medulla, Science **109**:534, 1949.
11. Goldenberg, M., Pines, K. L., Baldwin, E. de F., Green, D. G., and Roh, C. E.: The Hemodynamic Response of Man to Nor-epinephrine and Epinephrine and its Relation to the Problem of Hypertension, Am. J. Med. **5**:792, 1948.
12. Goldenberg, M., Apgar, V., Deterling, R., and Pines, K. L.: Nor-epinephrine (Arterenol Rx Sympathin N) as a Pressor Drug, J. A. M. A. **140**:776, 1949.
13. Garb, S.: Inotropic Action of Epinephrine, Nor-epinephrine, and N-isopropylnorepinephrine on Heart Muscle. Proc. Soc. Exper. Biol. & Med. **73**:134, 1950.
14. Wiggers, C. J.: Physiology in Health and Disease, ed. 3, Philadelphia, 1939, Lea & Febiger.
15. Starr, I., Gamble, C. J., Margolis, A., Donal, J. C., Jr., Joseph, N., and Eagle, E. A.: Clinical Study of the Action of Ten Commonly Used Drugs on Cardiac Output, Work and Size; on Respiration, on Metabolic Rate and on the Electrocardiogram, J. Clin. Investigation **16**:799, 1937.
16. Altschule, M. D., and Iglauer, A.: The Effect of Benzedrine and Paredrine on the Circulation, Metabolism, and Respiration in Normal Man, J. Clin. Investigation **19**:497, 1940.
17. Nathanson, M. H., and Miller, H.: The Action of Nor-epinephrine and of Epinephrine on the Ventricular Rate of Heart Block, AM. HEART J. **40**:375, 1950.
18. Garb, S., and Chenoweth, M. B.: Studies on Hydrocarbon-epinephrine Induced Ventricular Fibrillation, J. Pharmacol. & Exper. Therap. **94**:12, 1948.
19. Hellerstein, H. K., Brofman, B. F., and Caskey, W. H.: Shock Accompanying Myocardial Infarction: Treatment With Pressor Amines, AM. HEART J. **44**:407, 1952.
20. Beck, C. S., Hahn, R. S., Leighninger, D. S., and McAllister, F. F.: Operation for Coronary Artery Disease, J. A. M. A. **147**:1726, 1951.
21. Hingson, R. A.: Personal communication.

SHOCK ACCOMPANYING MYOCARDIAL INFARCTION: TREATMENT WITH PRESSOR AMINES

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THE TREATMENT of shock accompanying myocardial infarction has not been adequately established although the shock state is recognized as an important cause of early death following myocardial infarction.[1-6,13] The transient moderate hypotension frequently found during the acute state of myocardial infarction is usually salutory. Whether this relative hypotension is due to a decreased cardiac output or is a "compensatory" peripheral vascular phenomenon, the work of the heart is consequently diminished. However, when the blood pressure reaches a low critical level and the clinical picture of shock appears, the prognosis becomes grave.

In a study of 538 patient attacks, death generally occurred when the systolic blood pressure fell below 80 mm. Hg.[1] In a similar series of 524 patients with myocardial infarction, shock occurred in 6.9 per cent and was associated with a mortality rate of 77.8 per cent.[2] The incidence of shock ranged up to 15 per cent with a mortality rate of 88 per cent.[3] In our own experience prior to the present report, there was a 10 per cent incidence of shock with a mortality of 80 per cent as compared to a total mortality of 21 per cent.

In view of the universally poor prognosis associated with this condition and the unimpressive results of transfusion and other therapy[28,33] we decided to evaluate the treatment of shock using a vasopressor substance. Mephentermine,* a synthetic pressor amine, was found in a preliminary study to be an effective safe pressor substance with little direct effect upon myocardial irritability in the doses employed.[10]

SELECTION OF MATERIAL AND METHODS

Controls.—In a preliminary control study, one hundred random cases of myocardial infarction admitted to this hospital in the year prior to the start of this study were analyzed. The various factors such as age, sex, incidence of failure, and mortality compared well with other recent large series.[1-3,11,12] Shock occurred in ten cases with a mortality rate of 80 per cent. The average duration from the onset of shock until death was seven hours. Two of these patients who

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*Marketed as Wyamine (Wyeth Incorporated, Philadelphia, Pa.). The drug used in this study was kindly supplied by Dr. Joseph Seifter, Wyeth Institute of Biochemistry.

died had received intravenous fluids and plasma with no improvement. Since the total mortality following acute myocardial infarction was 21 per cent, the shock state occurred in 38 per cent of the deaths. This attests to the importance of shock as a factor in the mortality of myocardial infarction.

Beginning July 1, 1949, on the Medical Service at University Hospitals of Cleveland, an attempt was made to administer mephentermine to each case of shock accompanying myocardial infarction. In each case treated there was a definite clinical history with electrocardiographic changes diagnostic of myocardial infarction.

In order to evaluate the treatment of the shock accompanying acute myocardial infarction, certain rigid criteria must be elaborated. For the purpose of this study, shock was considered to exist in those patients who sustained hypotension (below 90 mm. Hg in previously normotensive patients) for more than one hour and during this time exhibited classical signs and symptoms of circulatory collapse, namely, rapid pulse (sinus tachycardia), small pulse pressure, pallid cyanosis, anxiety, thirst, faintness, cold moist skin, and stupor or coma. Patients exhibiting severe hypotension without clinical signs, as well as those exhibiting clinical signs without significant fall in blood pressure, were not considered to satisfy the criteria for shock and were excluded.

A total of eighteen cases were treated in this series. Three patients (Cases 2, 5, and 11) received mephentermine and ephedrine and another (Case 7) received ephedrine alone. One patient (Case 3) was given 300 c.c. plasma in a subsequent episode of hypotension. The others received mephentermine alone; no other pressor substance was used. Oxygen and digitalis were administered when indicated. In most instances serial electrocardiograms were obtained with a Sanborn Viso-Cardiette prior to and during the course of vasopressor therapy.

The intravenous route was considered advisable, in view of decreased circulation and poor absorption. The pressor substance was administered intravenously in 5 to 20 mg. doses or by slow intravenous drip of approximately 1 mg. per minute until a sufficient pressor response was produced. In a few cases the intramuscular route was used, usually in 35 mg. doses. It was deemed undesirable to produce a marked pressor response. Usually we attempted to maintain the systemic systolic blood pressure at approximately 100 mg. Hg. Generally, repeated administration of the pressor drug was necessary over a period of one to ten hours before the blood pressure was maintained.

RESULTS

Eighteen patients with myocardial infarction and shock were treated with pressor amines and other supportive measures. There were ten women and eight men, reflecting a disproportionate number of women for an infarction series. The ages ranged from 47 to 89 years with an average of 69 years. Electrocardiographically, the infarct was situated predominantly in the anterior wall in twelve and in the posterior wall in six. The infarcts were massive as indicated by precordial leads, and in a few cases at post-mortem examination.

The clinical picture of shock supervened on the first day of infarction in ten patients, on the second day in two, third day in three, and fifth day in three patients. Of the eighteen patients, six were hypertensive prior to the onset of the episode of myocardial infarction. Although shock may occur at a higher level in patients previously hypertensive, this was apparently not the case in this series.

The duration of shock ranged from one to twenty-four hours, being less than four hours in ten patients. Later in the study, vigorous pressor therapy was urged earlier in the shock period. Of three patients with shock less than two hours before treatment, two survived.

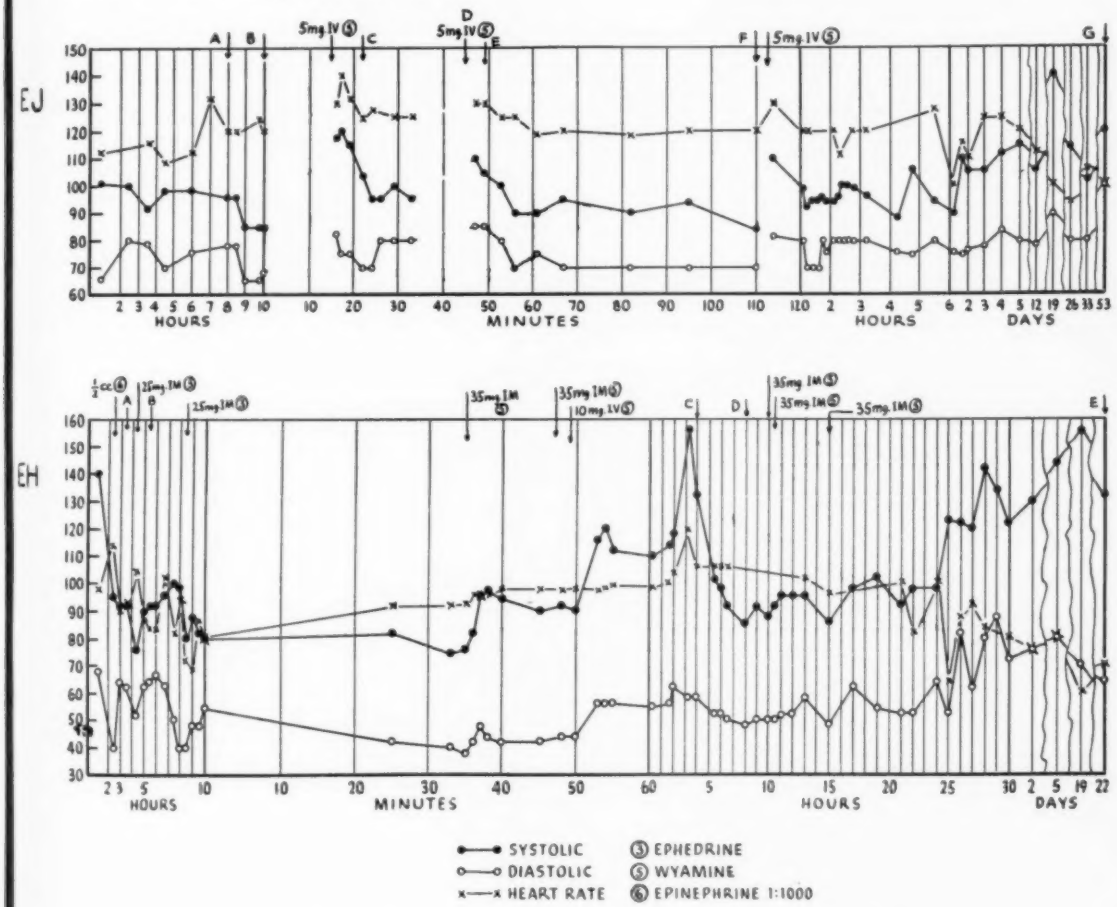

Fig. 1.—Case 1 (E. J.), a 65-year-old white woman. (In this and subsequent figures pertinent events are indicated by letters and injection of mephentermine and other drugs by appropriate numbers as shown on the graph. Interruption of blood pressure lines indicates that pressure was not obtainable.) *A*, Patient cyanotic, comatose, skin cold and clammy. *B*, Appears terminal, only occasional palpable beats for next 15 minutes. *C*, Clinically improved. *D*, Twenty minutes later, again coma and shock. *E*, Clinically improved. Blood pressure fell temporarily to 90 mm. Hg, but remained above 90 for the next forty minutes. *F*, Pulse feeble, slight cyanosis, evidence of shock. A more sustained response followed a third injection. *G*, Discharged on fifty-third hospital day.

Case 2 (E. H.), a 74-year-old white woman, previously known hypertensive for many years. *A*, Pulse irregular, patient cyanotic and lethargic. *B*, Pulse regular, color improved, then progressive appearance of shock. *C*, Color good, clinically improved, temperature 40° C. *D*, Patient complaining of thirst. *E*, Discharged on twenty-eighth hospital day.

TABLE I. RESULTS OF PRESSOR DRUG THERAPY ON EIGHTEEN PATIENTS WITH SHOCK ACCOMPANYING ACUTE MYOCARDIAL INFARCTION

CASE NUMBER	AGE (YRS)	COLOR SEX	DAY OF INFARCT	SITE OF INFARCT	DURATION SHOCK BEFORE TREATMENT (HRS.)	SEVERITY OF SHOCK + TO ++++	TREATMENT (MEPHENTERMINE)	BLOOD PRESSURE RESPONSE	REMARKS
Group A. Recovery From Shock and Acute Infarction With Discharge From Hospital									
1. E. J.	65	W F	1	Anterior	3	++++	5 mg. IV x 3 in 100 min.	0 → 120/75	
2. E. H.	74	W F	1	Anterior	7 +	+++	Ephedrine 25 mg. x 2 35 mg. IM x 4, 10 mg. IV	74/40 → 96/48 92/44 → 120/56	
3. P. T.	62	W M	3	Posterior	3	+++	5, 10, 42 mg. IV	0 → 96/74	
4. Y. E.	74	W F	2	Anterior	1.5	++	Strophanthin 0.5 mg. 15 mg. IV	90/60 → 122/78	
5. M. P.	68	W F	1	Anterior	2 +	+++	17.5 mg. IM x 2 Ephedrine 25 mg. IM	0 → 94/74	
6. L. G.	57	W F	3	Anterior	4	+++	5, 10, 12, 30 mg. IV in 1 hour	78/56 → 96/60	
7. L. J.	47	N M	1	Anterior	1	++++	Ephedrine 25 mg. IM	70/20 → 150/105	

Group B. Recovery From Shock, Death Due to Secondary Complications

8. J. C.	58	W M	1	Posterior	2	++++	35 mg. IM x 10	80/60 → 116/96	Died 26th hospital day. Congestive failure and extension of infarct
9. M. T.	84	W M	5	Anterior	2	+++	60 mg. IV in 24 hours	90/60 → 110/70	Sudden death on 10th hospital day
10. L. W.	80	W F	5	Anterior	2	+++	10 mg. IV, 35 mg. IM	90/50 → 120/90	Sudden death on 7th hospital day
11. F. W.	63	W M	1	Posterior	4	+++	10 mg. IV Ephedrine 25 mg. IM x 6	78/50 → 96/50	Died on 9th hospital day in uremia and congestive failure
12. E. S.	72	W F	5	Anterior	1	+++	10, 20 mg. IV, then 70 mg. IV	84/70 → 160/80 0 → 100/64	Died on 7th hospital day, rupture of ventricle
13. P. R.	89	W M	1	Anterior	6 +	++++	10 mg. IV	75/50 → 92/60	Died on 3rd hospital day in uremia
14. N. P.	84	W F	1	Posterior	2 +	++++	35 mg. IV, then 100 mg. IV in 2 hours	0 → 110/70	Died on 3rd hospital day in congestive failure and uremia

Group C. Poor Response, Death Within Twelve Hours of Therapy

15. C. H.	65	W F	1	Anterior	6 +	++++	10 mg., 25 mg. IV x 3	0 → 75/50	Died 3 hours later in ventricular fibrillation
16. M. L.	70	W F	3	Posterior	24 +	++++	35 mg. IM	78/58 → 100/78	Recovered from shock, died 12 hours later
17. J. K.	78	W M	2	Anterior	5	++++	40 mg. IV in 45 min.	0 → 70/59	Sudden death 2 hours later
18. A. L.	52	W M	1	Posterior	2	+++	105 mg. IV in 2 hours	0 → 110/80	Recovered from shock, died suddenly 1 hour later

Table I represents the pertinent data and the results of pressor amine therapy in the three groups. Figs. 1 to 4 illustrate typical responses. Abstracts of the case histories are appended. Of the eighteen patients in shock, a satisfactory result was obtained in fourteen. Seven patients (39 per cent) emerged from the state of shock and were ultimately discharged from the hospital (Group A). Another seven (39 per cent), although recovering from the initial state of shock, succumbed to secondary complications two to twenty-six days later (average seven days) (Group B). In only four cases (22 per cent) did death occur within twelve hours of pressor amine therapy (Group C). Two of these patients had shown dramatic temporary improvement.

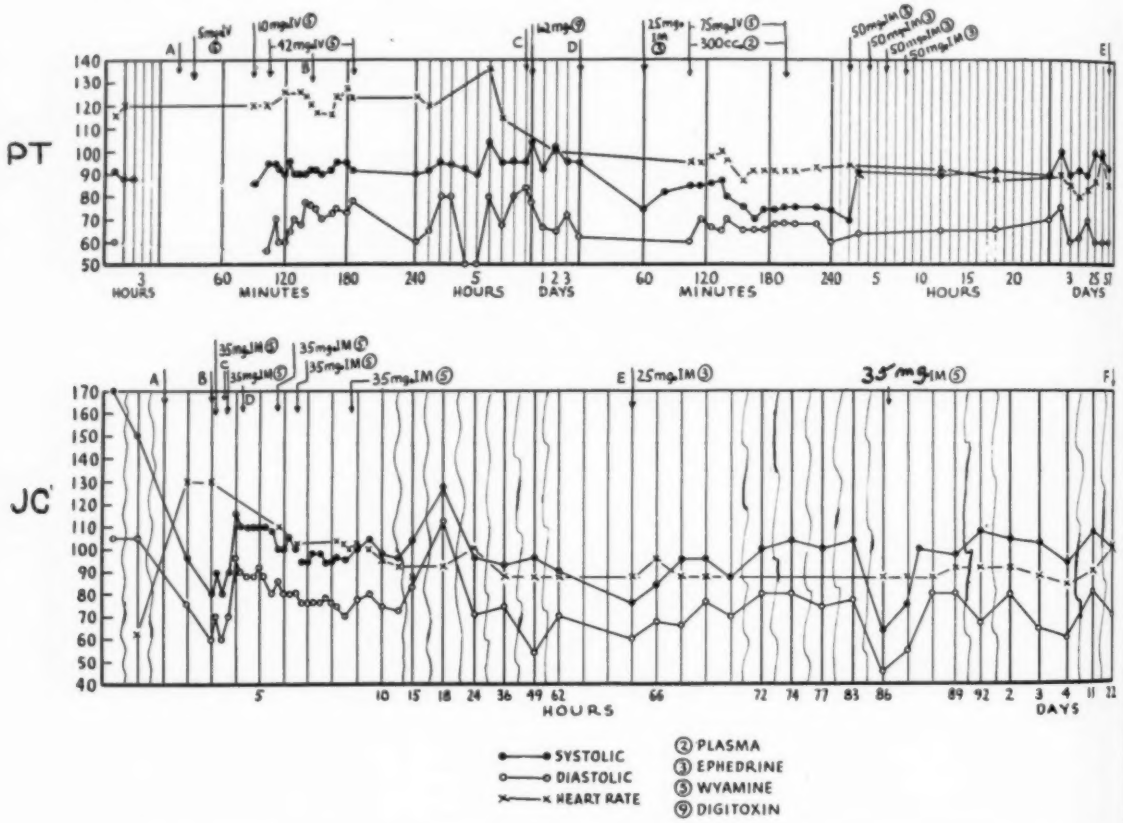

Fig. 2.—Case 3 (P. T.), a 62-year-old white man. *A*, Emesis, in shock, pulse unobtainable. *B*, Clinically improved, respirations good, out of shock. *C*, Marked dyspnea, mild diabetic ketosis noted, small doses of regular insulin started. *D*, Apprehensive, restless, cold perspiration followed by fall in blood pressure to shock level within next hour with delayed response to more pressor therapy. *E*, Discharged on sixty-fifth hospital day with congestive failure.

Case 8 (J. C.), a 58-year-old white man. Known hypertensive for at least three years (170/105). *A*, Perspiring profusely, vomiting. *B*, In shock, cold clammy skin. *C*, Severe shock. *D*, Clinically improved, less apprehension. *E*, Perspiring, distressed, followed by recurrent hypotension on sixty-fourth and eighty-sixth hours responding to therapy. *F*, Sudden death on twenty-sixth hospital day.

Congestive Failure.—In a majority of these patients (twelve of eighteen) evidence of congestive failure was present at the time of shock, (usually basal râles and cervical venous distention) (Table II). However, six of the twelve had congestive failure before the infarct. In three of these the degree of failure was greater at the time of shock. The presence of failure prior to the infarct did not appear to have an adverse influence upon the outcome, since three of six such patients survived. On the other hand, failure occurring for the first time, associated with the shock episode, was associated with a higher mortality, only one of six such patients surviving.

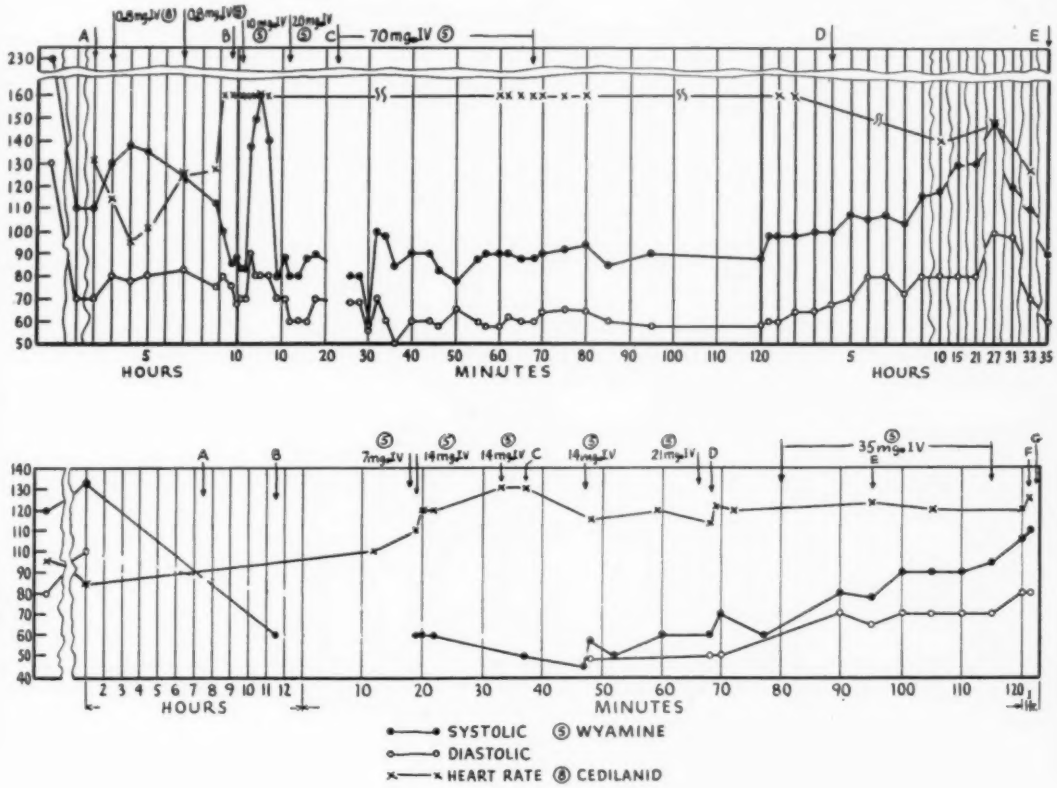

Fig. 3.—Case 12 (E. S.), a 79-year-old white woman. Known hypertensive (230/130) for many years. *A*, Auricular fibrillation, cyanosis, dyspnea, in oxygen tent, average ventricular rate was 130, unmodified by 1.6 mg. intravenous Cedilanid. *B*, Shock present, respirations rapid and shallow, cold and clammy skin, average ventricular rate 160. *C*, Patient appears terminal, comatose. *D*, Clinically improved. *E*, Sudden death on second hospital day.

Case 18 (A. L.), a 52-year-old white man, being evaluated for coronary insufficiency. *A*, Priodax given for gall bladder series. *B*, Loose stool, nausea, vomiting, then shock, diastolic pressure not obtainable, electrocardiogram shows acute posterior infarct and severe myocardial ischemia. *C*, Substernal pain. *D*, Heart sounds of better quality. *E*, Patient alert and talking; serial electrocardiograms show decreasing myocardial ischemia. *F*, Crisis appears over; electrocardiograph shows posterior infarct. *G*, Sudden death.

TABLE II. RELATIONSHIP OF CONGESTIVE FAILURE TO SHOCK ACCOMPANYING ACUTE MYOCARDIAL INFARCTION

CASE NUMBER	PREINFARCT BLOOD PRESSURE N = NORMOTENSIVE H = HYPERTENSIVE	FAILURE PRIOR TO INFARCT		FAILURE AT TIME OF SHOCK		STATUS AFTER TREATMENT OF SHOCK
		SEVERITY 0 TO ++	TYPE	SEVERITY 0 TO ++	TYPE	
Group A						
1.	N	0	—	+	Cyanosis, few râles	8 days later increased pulmonary congestion. Digitoxin given
2.	H	+	On digitalis. Dyspnea and ankle edema	++	Cyanosis, râles, ankle edema	Digitalis continued, failure decreased
3.	N	+	Ankle edema	+	Liver down 3 finger-breaths, few râles	Congestion worse in 24 hours. Digitoxin required
4.	H	+	Veins distended. On digitalis	++	Alternans. Pulmonary edema	Improved. On maintenance digitalis
5.	N	0	—	0	—	No failure
6.	N	0	On digitalis for auricular fibrillation	0	—	No failure. On digitalis for auricular fibrillation
7.	H	0	—	0	—	No failure

Group B 8.	H	0	—	+	Râles	4 wks. later, pulmonary edema. Digitalis required
9.	H	0	—	0	—	No failure
10.	N	0	—	+	Râles at both bases. No digitalis	No increase in failure
11.	N	+	Dyspnea	+	Râles at bases	Râles persisted
12.	N	0	—	+	Right basal râles	Râles persisted
13.	N	0	—	+	Basal râles	Râles persisted
14.	H	+	Pulmonary edema; pedal edema	++	Râles, hepatomegaly, pedal edema	Worse. Died in failure. Digitalized on admission
Group C 15.	N	0	—	+	Venous distention	—
16.	N	+	Cough, râles, liver down	+	Venous distention	Persisted
17.	N	0	—	0	—	No failure
18.	N	0	—	0	—	No failure

Pressor therapy did not produce congestive failure in patients not previously in failure, nor was there evidence of aggravation of the pre-existing failure. In three patients developing increased pulmonary congestion one, eight, and twenty-four days after emergence from shock, the delayed appearance of such signs can hardly be ascribed to pressor therapy.

Ectopic rhythms were not produced by pressor therapy. In several cases, there was electrocardiographic evidence of diminution of myocardial ischemia during the pressor response.

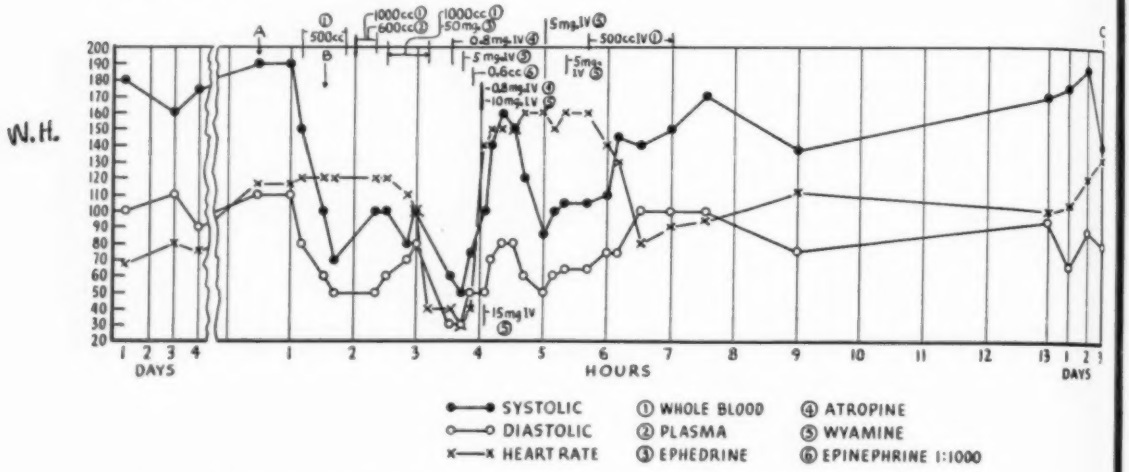

Fig. 4.—Effect of mephentermine in surgical hypotension due to massive blood loss, associated with myocardial ischemia. W. H., a 66-year-old white man with adenocarcinoma of colon. *A*, Under gas-oxygen-ether anesthesia for resection of splenic flexure of colon. *B*, Massive bleeding, whole blood and plasma transfusions started. Electrocardiogram taken at fourth hour shows pattern of acute posterior infarction. Serial electrocardiograms were taken during restoration of blood pressure (Fig. 5). *C*, Patient never regained consciousness; death on third day. (Discussion in text.)

DISCUSSION

During the acute stage of myocardial infarction, transient moderate hypotension is frequent and is usually considered salutory.[13] However, if the blood pressure falls to a critical level for a sufficient time, the clinical picture of shock supervenes, and the prognosis becomes grave.

The etiology of shock accompanying myocardial infarction is still obscure. Although the shock with myocardial infarction may produce a clinical picture similar to that of traumatic or hemorrhagic shock, the greatest etiological difference is the initiating cardiac insult present in the former. After coronary occlusion a significant portion of the ischemic ventricular myocardium is deleted within a few minutes,[8,14,15] thereby throwing the burden of ventricular work on the remaining muscle. Hypodynamic contractions and cardiac dilatation may supervene unless full compensatory reactions of the remaining fractions are brought into play.[15] If sufficient myocardium survives, dynamics return to normal, with restoration of adequate cardiac output and circulatory balance.

As a consequence of reduced cardiac output[16,17] and other less known factors, a severe reduction in systemic blood pressure may ensue during the period of

hypodynamic contractions. The coronary blood flow and collateral intercoronary anastomoses are thereby reduced.[8] The resultant myocardial depression[18] contributes further to the circulatory failure. Experimentally, hypotension increases the area of ballooning produced by coronary occlusion.[8] Furthermore, when blood pressure is lowered in a dog with a constricted but not occluded coronary artery, contractility ceases in the area supplied by that artery. After restoration of the blood pressure, normal contractility returns.

In patients with coronary arteriosclerosis and acute coronary occlusion, hypotension, from whatever cause, produces ischemia in large segments of myocardium supplied by the stenotic coronary arteries. Also, patients with coronary arteriosclerosis may develop acute coronary insufficiency as a result of hemorrhage and hypotension.[19,20]

The degree of myocardial ischemia which may be produced and its abolition are dramatically demonstrated in Figs. 4 and 5. During the course of a surgical operation, severe hemorrhage produced a drastic fall in blood pressure. An electrocardiogram taken before restitution of the blood pressure was diagnostic of acute posterior myocardial infarction. Whole blood and mephentermine finally restored the blood pressure[10] with rapid disappearance of evidence of myocardial infarction.

Reduction of cardiac output is a consistent finding in shock with infarction.[17,21,32] Blood and plasma volume are not immediately reduced, but later may be the result of dehydration due to sweating or vomiting.[21] The degree of reduction of circulating blood volume per se is insufficient to produce the picture of shock.[21,72] Usually there is no evidence of failure of the right ventricle (the peripheral and central venous pressures are not elevated). However, in a majority of patients (and in experimental occlusion in dogs[23]) there is some indication of incompetence of the left ventricle. There is evidence of elevation of left atrial and pulmonary venous pressures: pulmonary congestion, râles, and prolonged circulation time.[24,25] Since venous return to the left ventricle is more than adequate, the fall in cardiac output with resultant shock cannot be attributed to the mechanisms that are thought to be important in traumatic shock. The predominant involvement of the left ventricle in myocardial infarction with relative competence of the right ventricle readily explains these changes. Congestive heart failure frequently accompanies shock in acute infarction, particularly when the patient previously had suffered from congestive failure or loss of cardiac reserve.[7,22] In such patients the increase of signs of congestion may predominate over those of shock.

The objective of therapy in shock accompanying myocardial infarction is to restore the effective head of blood pressure in the aorta to perfuse adequately the coronary, cerebral, renal, hepatic, and other vital circulations. The measures designed to combat shock are directed toward supporting the uninfarcted muscle. Elevation of the blood pressure (to 100 mm. Hg systolic in patients who were previously normotensive, and 120 mm. in those previously hypertensive) improves the total coronary circulation, enhances the chances of survival of borderline myocardium and that supplied by stenotic arteries, and may decrease the size of

the infarct. In many patients, the area of ischemic myocardium is relatively so large that death is inevitable regardless of the treatment. Similarly, there are some with moderate hypotension who recover without specific medication. Between these two extremes, there are many patients in whom the treatment of shock may be lifesaving.

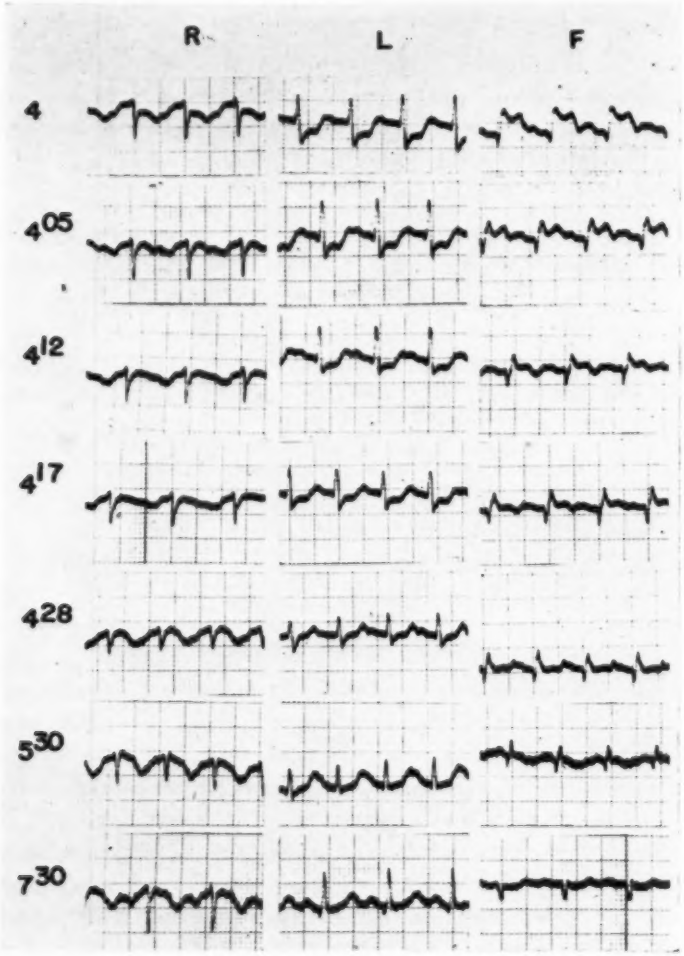

Fig. 5.—(W. H.) Serial electrocardiograms. Leads R, L, and F, showing rapid evolution of characteristic changes of posterior infarct during restoration of blood pressure. Note marked ST-T elevation in F and depression in L at time corresponding to the fourth hour on Fig. 4. At 7.5 hours all evidence of ischemia had disappeared. At autopsy, there was no evidence of coronary occlusion or myocardial infarction. (Discussion in text.)

A suggested rational therapy at the present time appears to be the use of vasopressor drugs and cardiac stimulants. The ideal pressor drug would elevate blood pressure, increase peripheral resistance, produce a proportionate increase of coronary flow, have minimal side effects, and would not decrease cardiac output or produce serious arrhythmias. Although the ideal pressor drug has not been identified as yet, some amines now available fulfill most of these requirements.

These include norepinephrine, mephentermine,[10] desoxyephedrine, ephedrine, Paredrine, Neosynephrine, and amphetamine. Objections are justifiably raised to the use of epinephrine which enhances the irritability of the myocardium sufficiently to produce serious ectopic rhythms. Whether there is an element of vasodilatation present or not,[32] peripheral vasoconstriction can be produced by the administration of pressor amines. All sympathomimetic amines in sufficiently large doses will produce ectopic rhythms. The metabolic effects of sympathomimetic amines consist of an increase of general and cardiac metabolism, and an anoxating effect on the myocardium.[26] The above amines have a lesser tendency to stimulate metabolism.[22] Although the anoxating effect is out of proportion to the increase of coronary flow, the elevation of systemic blood pressure and coronary flow probably outweigh the apparent disadvantages. Large increases of coronary flow may occur without significant changes in heart rate or aortic pressure.[27] With the elevation of aortic pressure there is further augmentation of basic coronary flow.

Pressor amines such as mephentermine can be used easily and safely. A definite pressor response is usually achieved rapidly without introducing complicating factors such as those associated with alteration of blood volume. Furthermore, the results of venous or retrograde arterial transfusions have been disappointing.[3,7,9,28,29,33]

The use of digitalis glycosides, particularly the rapidly acting ones (strophanthin, ouabain, Digoxin, etc.) is valid[25] particularly when there is evidence of congestive failure even in patients with predominant signs of shock. Strophanthin increases cardiac output, efficiency, and peripheral blood pressure within a few minutes.[30] The danger of enhancing ventricular irritability to produce ventricular fibrillation occurs only with excessive amounts.[31] Likewise, cardiac rupture is unlikely since this complication occurs from the fourth to seventh day, and shock usually occurs earlier.

COMMENT

The treatment of shock due to myocardial infarction rests upon a firm clinical basis. There is need for vigorous early treatment to restore an effective head of blood pressure. An elevation of blood pressure can be produced by pressor amines and is usually associated with clinical improvement. Although a statistical analysis of this small series was not attempted, the results appear significant. Fourteen of the eighteen patients emerged from the shock state for a minimum period of two days, and seven were eventually discharged from the hospital. The more favorable results of pressor therapy in comparison to other methods justify further clinical application in the treatment of shock accompanying myocardial infarction.

SUMMARY

1. Shock accompanying myocardial infarction is associated with a mortality of approximately 80 per cent.

2. Pressor amines were administered to eighteen patients in shock accompanying myocardial infarction.* Mephentermine (Wyamine), in a preliminary study, was found to be a safe effective pressor substance with little direct effect upon myocardial irritability in the doses employed. Seventeen patients were treated with mephentermine (three also received ephedrine) and one received ephedrine alone.

3. A pressor response was produced in sixteen patients. Fourteen emerged from the shock state with marked clinical improvement for more than two days. However, seven succumbed to secondary complications two to twenty-six days later. Seven patients recovered sufficiently to be discharged from the hospital.

4. Pressor therapy did not produce congestive failure in patients not previously in failure, nor did it aggravate pre-existing failure.

5. The use of pressor amines in the treatment of shock accompanying myocardial infarction appears to rest upon a firm clinical basis.

CASE REPORTS

CASE 1.—(Fig. 1) E. J., a 55-year-old white woman, was admitted to the hospital on Jan. 8, 1950, with a history of crushing substernal pain of five hours' duration. An electrocardiogram showed a large anterior infarct. Prior to the admission the patient was known to have had a normal blood pressure and had never been in congestive heart failure. On admission the blood pressure was found to be 102/66 mm. Hg with a heart rate of 112 per minute. Eight hours after admission the blood pressure was 96/78 mm. Hg with a heart rate of 120. The patient was cyanotic, comatose, and the skin was cold and clammy; respirations were slow and labored. Ten hours after admission the blood pressure had fallen to 85/68 mm. Hg, and the patient appeared moribund. A few minutes later the blood pressure was unobtainable and only occasional beats could be palpated in the radial pulse. Intravenous mephentermine, 5 mg., produced a rapid rise of blood pressure to 120/75 mm. Hg within two minutes. There was remarkable improvement in the patient's clinical condition. The patient became aware of her surroundings and began to moan. The blood pressure remained above 90 systolic for thirty minutes and then abruptly fell and became imperceptible. Coma and cyanosis supervened. Another dose of mephentermine, 5 mg. intravenously, produced a rise of blood pressure to 110/85 within one minute; again there was marked clinical improvement. One hour later there was some deterioration of the patient's condition; the pulse became feeble and there was again evidence of shock. Five milligrams of mephentermine were again given intravenously with an abrupt rise of blood pressure and further clinical improvement. Thereafter the blood pressure was maintained above 90 mm. Hg systolic. There was gradual clinical improvement, and the patient was subsequently discharged on her fifty-third hospital day. During the period of shock there had been some evidence of congestive failure manifested by cyanosis and râles at the bases of the lungs. Eight days later increased pulmonary congestion occurred and the patient was digitalized with good results. Her private physician reported that the patient lived an active life for the following ten months. She died suddenly, probably of a second thrombosis eleven months after the acute infarct.

CASE 2.—(Fig. 1) E. H., a 74-year-old white woman, was admitted to the hospital on May 4, 1950, with a history of sudden onset of abdominal pain, dyspnea, and loss of consciousness. When seen by her private physician the pulse and heart sounds were unobtainable. One cubic centimeter of epinephrine, 1:1000, was administered intracardially and the patient was brought to the hospital in a respirator. The patient had previously been known to be hypertensive and had been in mild congestive failure manifested by dyspnea and ankle edema for which she had been receiving digitalis. The blood pressure at the time of admission was 140/68 mm. Hg with a heart rate of 98. The patient was semistuporous and cyanotic. Electrocardiography showed acute

*Since this study was completed, an additional three patients with shock accompanying myocardial infarction were successfully treated with pressor drugs and survived.

anterior myocardial infarction and left bundle branch block. Two hours after admission the blood pressure had fallen to 95/40 mm. Hg with a heart rate of 112. The patient was cold and clammy and appeared to be in shock. Epinephrine (0.5 c.c.) was given subcutaneously but there was little effect. Four hours after admission the blood pressure had fallen to 76/52 mm. Hg with a heart rate of 104. Twenty-five milligrams of ephedrine was given intramuscularly. The blood pressure gradually rose to 90/62 mm. Hg with a heart rate of 88, and the patient appeared clinically better. Seven hours after admission the blood pressure had again fallen to 80/40 mm. Hg with a heart rate of 72, and 25 mg. of ephedrine were again given; at that time there was little improvement. The blood pressure continued to fall to 74/40 mm. Hg at which time mephentermine, 25 mg., was given intramuscularly, followed by a rise of blood pressure to 96/48 mm. Hg in two minutes with clinical improvement. Twelve minutes later 35 mg. were given intramuscularly followed by 10 mg. intravenously with a marked pressor response and further clinical improvement. Eight hours later the blood pressure was 86/48 mm. Hg and the patient appeared worse. Thirty-five milligram doses were given at half-hour intervals for two doses with a rise in blood pressure to 96/58 mm. Hg. Five hours later the blood pressure had again fallen to 86/48 mm. Hg. with a heart rate of 96, and another 35 mg. dose of mephentermine was given; there was a subsequent rise in blood pressure with improvement in the patient's clinical condition. After this episode the blood pressure was maintained at approximately 130/50 to 115/70 mm. Hg. There was gradual clinical improvement and the patient was discharged on the twenty-eighth hospital day. She is alive and well at the time of this report. During the period of shock there appeared to be some increase in the degree of congestive failure, manifested by cyanosis, râles, and ankle edema. Subsequently, the digitalis was continued and there was a decrease in the degree of congestive failure at the time of discharge.

Case 3.—(Fig. 2) P. T., a 62-year-old white man, was admitted to the hospital on April 29, 1950, with a history of substernal pressure for three days accompanied by dyspnea, nausea, and vomiting. The patient was known to have had myocardial infarcts on two occasions, six and seven years prior to admission. There was no history of previous hypertension. There had been mild congestive failure manifested by ankle edema. On admission the blood pressure was 92/60 mm. Hg with a heart rate of 116. An electrocardiogram showed right bundle branch block, and a recent posterior infarct. The patient was extremely weak and short of breath; the heart sounds were inaudible and the patient appeared to be in shock. Two hours after admission the blood pressure had fallen to 88/60 mm. Hg and five hours after admission, following a period of vomiting, the blood pressure and pulse were unobtainable; 5 mg. of mephentermine given intravenously produced no effect. Six hours after admission systolic blood pressure was 85 mm. Hg; 10 mg. of mephentermine were given intravenously, followed by a slow intravenous drip of 42 mg. over a period of eighty minutes. During this period the systolic pressure rose to 96/64 mm. Hg, and subsequently to 96/74 mm. Hg with marked clinical improvement in the patient's condition, and emergence from the shock state. The blood pressure was then maintained at approximately 100 mm. Hg systolic for the next five days. On the day following admission the patient's degree of congestive failure increased. The liver edge was 3 cm. below the costal margin; there were râles at both bases. Digitalis was administered. The patient was found to be in mild diabetic ketosis, which was controlled with small doses of insulin. On the fifth hospital day the blood pressure suddenly fell to 70 mm. Hg systolic, and the patient appeared to be in shock; 25 mg. of ephederine gave some pressor response; 75 mg. of mephentermine plus 300 c.c. of plasma intravenously were given over the next ninety minutes. However, the blood pressure continued to fall reaching 74/68 mm. Hg. Subsequently, ephederine, 50 mg. intramuscularly, was given at two-hour intervals for four doses. The blood pressure stabilized at 90 mm. Hg systolic without further therapy and was maintained until the patient's discharge from the hospital on his sixty-fifth hospital day. At this time his congestive failure was well controlled on digitoxin, and his diabetes was regulated by diet alone.

Case 4.—Y. E., a 74-year-old white woman, was admitted to the hospital with the sudden onset of substernal pain on the day of admission. The patient was a known diabetic and hypertensive of long standing. At the time of admission the blood pressure was 130/90 mm. Hg with a heart rate of 140, and the patient appeared seriously ill; she was cyanotic and responded only to painful stimuli. An electrocardiogram showed changes consistent with a recent anterior myo-

cardial infarction. On the morning following admission the blood pressure had fallen to 120/70 and then to 90/60 mm. Hg with a heart rate of 88. At the time of admission she had been in acute left ventricular failure. Pressure oxygen and tourniquets had been administered. Strophanthin, 0.35 mg., was given intravenously with good response. However, when the pressure had fallen to 90/60 mm. Hg, the patient appeared to be in shock; she was cyanotic and there was cold clammy perspiration. Mephentermine, 15 mg., was given intravenously with a prompt rise in blood pressure to 110/68 mm. Hg in three minutes; the heart rate rose to 96. Ten minutes after the mephentermine administration the blood pressure had risen to 142/60 mm. Hg with a heart rate of 96. There was dramatic clinical improvement at this time, and the blood pressure was subsequently maintained at approximately 130 to 160 mm. Hg systolic. Although the patient was seriously ill throughout her hospital course, she was eventually discharged five weeks after admission, only to be admitted two weeks later in a terminal condition, at which time she died presumably of a recurrent coronary occlusion. At the time of her discharge her congestive failure was well controlled on maintenance digitalis.

CASE 5.—M. P., a 68-year-old white woman, was admitted to the hospital on Dec. 28, 1950, with a history of sudden onset of acute epigastric pain. An electrocardiogram showed an acute anterior infarct. At the time of admission the blood pressure was unobtainable and she was immediately given 17.5 mg. of mephentermine intramuscularly. Within five minutes the blood pressure had risen to 97/74 mm. Hg, and the patient improved somewhat from her state of severe shock. The pressure was maintained at 90/60 mm. Hg with heart rate of 160 for one-half hour, at which point it gradually declined to 70/60 mm. Hg, and again 17.5 mg. of mephentermine was given intramuscularly. Again there was a pressor response, the pressure rising to 90/70 mm. Hg, with a heart rate of 108. For the next twenty-four hours the blood pressure was fairly well maintained with 17.5 mg. of mephentermine given intramuscularly every two hours. Throughout the next week of hospitalization there was a tendency for the systolic blood pressure to drop below 90 mm. Hg daily. In each instance the administration of mephentermine or ephedrine gave a similar pressor response. The blood pressure was then well maintained over 100 mm. Hg systolic throughout the next three weeks of hospitalization and the patient was discharged in good condition. This patient had previously been known to be normotensive. At no time during her episode of infarction had any evidence of congestive failure been present.

CASE 6.—L. G., a 57-year-old white woman, was admitted to the hospital on July 8, 1950, with a history of acute anterior chest pain. The electrocardiogram showed auricular fibrillation and a recent anterior myocardial infarction. At the time of admission the blood pressure was 78/56 mm. Hg, and the heart rate 106. Clinically the patient was in shock. The skin was cold and clammy and there was cyanosis; 5 mg. of mephentermine were given intravenously. The blood pressure rose to 96/60 mm. Hg in two minutes; the pulse rate remained constant. Within a few minutes, the blood pressure again fell to 70 mm. Hg systolic; 10 mg. of mephentermine intravenously produced a rise to 84/66 mm. Hg. However, the pressure then gradually fell to 70/50 mm. Hg and the patient appeared to be in extremis. Twelve milligrams of mephentermine intravenously followed by an intravenous drip of 30 mg. over a sixty-minute period raised the blood pressure to 80/64 mm. Hg. The heart rate remained at approximately 105. For the next two days the patient was maintained without pressor drugs, the systolic pressure remaining above 80 mm. Hg. The patient was subsequently digitalized, primarily because of the rapid ventricular rate. There was gradual improvement over the next two weeks, the blood pressure gradually returning to a level of 110/70 mm. Hg. The patient, much improved, was discharged on her twenty-ninth hospital day. Although the patient received digitalis in order to control auricular fibrillation, there was no evidence of congestive failure in this case.

CASE 7.—L. J., a 47-year-old Negro man, was admitted to the hospital on Feb. 26, 1951, for routine diagnostic study of essential hypertension. On admission the blood pressure was 220/110 mm. Hg. On the fifth hospital day as the patient was dressing to go home he complained of sudden weakness and inability to get his breath. There was profuse diaphoresis; the pulse was imperceptible, and the patient suddenly became unresponsive. The blood pressure was found to have fallen to 100/60 mm. Hg and rapidly fell to 70/20 mm. Hg despite morphine and oxygen administration. One hour after the onset of this shock state, he was given ephedrine sulfate,

25 mg., intramuscularly, with a dramatic rise in blood pressure within five minutes to 150/105 mm. Hg, and then in one hour to 225/125 mm. Hg with marked clinical improvement. An emergency electrocardiogram showed a massive posterior myocardial infarction. Following this acute episode of shock, the blood pressure remained at the previous hypertensive level, and the patient was ultimately discharged on the forty-ninth hospital day. He was subsequently admitted six months later with an acute anterior infarction from which he recovered.

CASE 8.—(Fig. 2) J. C., a 58-year-old white man, was admitted to the hospital on Nov. 17, 1949, with a history of sudden onset of severe chest pain, faintness, and cyanosis. He had previously been a known hypertensive with a blood pressure of 170/105 mm. Hg in 1946. On admission the blood pressure was 150/105 mm. Hg with a heart rate of 62. An electrocardiogram revealed an acute posterior infarct and right bundle branch block. Twelve hours after admission the patient suddenly became acutely ill and the blood pressure fell to 96/60 mm. Hg with a heart rate rising to 130. One hour later the pressure had fallen progressively to 80/60 mm. Hg with a heart rate of 130, and the patient was in severe shock. Mephentermine, 35 mg., was given intramuscularly, and in ten minutes the pressure had risen to 90/70 mm. Hg, but gradually fell to 80/60 mm. Hg, and again mephentermine, 35 mg., was given intramuscularly. This was followed by a rise in blood pressure to 116/96 mm. Hg and the patient showed dramatic clinical improvement. Booster doses of mephentermine, 35 mg., were given intramuscularly at approximately hourly intervals for three doses thereafter, and the blood pressure was maintained at approximately 100 mm. Hg systolic. The patient's color was good and he was relatively comfortable. During the next three nights, the patient had episodes of hypotension of a transitory nature. However, on the fifth hospital day the pressure suddenly fell to 64/45 mm. Hg, and the patient was again in clinical shock; 35 mg. of mephentermine were given intramuscularly, and the pressure was maintained at 108/68 mm. Hg with a heart rate of 100. At the time of admission the patient had râles in both bases. On the twenty-first hospital day the patient developed pulmonary edema, and was digitalized with good results. On the twenty-sixth hospital day the patient died suddenly. Post-mortem examination revealed a recent infarct of the interventricular septum, and multiple recent thromboses of the anterior branch of the left coronary, and also of the right main coronary artery. There was chronic passive hyperemia of the liver, kidneys, spleen and lungs, and bilateral pleural effusion.

CASE 9.—M. T., an 84-year-old white man, was admitted to the hospital with a history of substernal and deep epigastric pain five days prior to admission. There was no previous history of hypertension or angina. At the time of admission on July 15, 1949, the patient did not appear seriously ill. The blood pressure was 150/100 mm. Hg with a rate of 80. Electrocardiography showed a recent massive anterior myocardial infarction and numerous premature ventricular beats. For the next fourteen hours the pressure remained unchanged; however, within two hours the blood pressure dropped to 90/60 mm. Hg and the patient appeared to be in shock with a feeble thready pulse and cold and clammy skin. The heart rate was 90. Administration of 2 mg. of mephentermine intravenously caused a rise of blood pressure to 110/80 mm. Hg and administration of small doses, usually less than 5 mg. per hour, was continued for the next ten hours, blood pressure being maintained at about 100 mm. Hg systolic. On the next day 2 mg. doses were given intramuscularly at frequent intervals and the blood pressure was maintained at 100/70 mm. Hg. When the mephentermine was discontinued for a two-hour period the pressure fell to 88/52 mm. Hg, and ashen cyanosis appeared. Small intravenous doses of mephentermine maintained the pressure at about 100 mm. Hg systolic, and the patient appeared clinically improved. Subsequently the pressure rose to 114/72 mm. Hg and then to 150/110 mm. Hg on the fourth hospital day where it was maintained for the next six days. However, on the tenth hospital day the patient suddenly died. Post-mortem examination revealed a massive recent infarct of the anterior myocardium, involving the septum. There was no evidence of congestive failure throughout this patient's hospital course.

CASE 10.—L. W., an 80-year-old white woman, was admitted to the hospital on Oct. 12, 1949, with a history of sudden onset of substernal chest pain. At the time of admission the blood pressure was 110/70 mm. Hg with a heart rate of 80 and an electrocardiogram showed massive recent anterior infarct. Blood pressure remained at this level until the third hospital day at which time it progressively fell to 90/50 mm. Hg. The patient was in a state of collapse and complained

of severe pain. There was spontaneous recovery from this state of collapse. However, on the fourth hospital day auricular fibrillation with a ventricular rate of 180 occurred and blood pressure fell to 70/50 mm. Hg. Spontaneously the mechanism reverted to a regular sinus rhythm in five hours. The blood pressure subsequently rose to 100/60 mm. Hg. On the fifth hospital day the patient again appeared to be in collapse with a blood pressure of 90/50 mm. Hg and a pulse of 78. Because of the poor appearance of the patient and the fear of further collapse, 10 mg. of mephentermine were given intravenously with a rise of blood pressure to 120/90 mm. Hg within five minutes, at which level it remained associated with marked clinical improvement for the next three hours. The pressure remained between 96/70 and 110/70 mm. Hg until the sixth hospital day at which time the patient suddenly went into shock although the blood pressure was 96/60 mm. Hg with a heart rate of 80. Mephentermine, 35 mg., was given intramuscularly with a gradual rise of blood pressure to 110/70 mm. Hg with a heart rate of 86, where it was maintained for the next twelve hours. On the seventh hospital day the patient died suddenly. Autopsy was not performed.

CASE 11.—F. W., a 63-year-old white man, was admitted to the hospital on Feb. 8, 1950, with a history of sudden onset of severe anterior chest pain with radiation down the left arm. The patient had a history of acute myocardial infarction in 1948 and had had angina in the intervening two years. At the time of admission the blood pressure was 94/58 mm. Hg with a heart rate of 50. The patient did not appear in great distress. An electrocardiogram showed a 2:1 atrioventricular block, left bundle branch block, and an acute posterior myocardial infarction. Eight hours after admission the patient's blood pressure had progressively dropped to 78/50 mm. Hg with a heart rate of 72. Respirations were labored; the pulse was weak and irregular. The simultaneous intravenous administration of 10 mg. of mephentermine and the intramuscular administration of 25 mg. of ephedrine sulfate caused the blood pressure to rise to 96/50 mm. Hg with a heart rate of 76, and the patient appeared clinically improved. Frequent doses of ephedrine were given to maintain the blood pressure at approximately 108 mm. Hg systolic for the first three hospital days. By the fifth hospital day the blood urea nitrogen had risen to 128 mg. per 100 c.c. The patient had developed bilateral pulmonary râles on the third hospital day and these increased somewhat. On the seventh hospital day the blood pressure which had stabilized around 110/70 mm. Hg dropped gradually to 90/60 mm. Hg and on the ninth hospital day the patient suddenly died. Post-mortem examination was not done.

CASE 12.—(Fig. 3) E. S., a 79-year-old white woman, known to have been hypertensive for many years, was admitted to the hospital on Sept. 27, 1950. The blood pressure was 230/130 mm. Hg one month prior to admission. She was acutely and severely ill. An electrocardiogram showed extensive acute anterior myocardial infarction; auricular fibrillation was present, with an average ventricular rate of 130. The blood pressure was 110/70 mm Hg. Cedilanid was administered intravenously with little effect upon the ventricular rate, even after a total dose of 1.6 mg. The blood pressure fell progressively so that nine hours after admission the pressure had fallen to 84/70 mm. Hg. The heart rate was 160 and the patient appeared to be in severe shock. Mephentermine, 10 mg., was given intravenously with a prompt pressor response, the blood pressure rising to 160/80 mm. Hg within four minutes. The pulse rate was unchanged. However, there was a rapid decline in blood pressure to 80/60 mm. Hg at which point 20 mg. of mephentermine was given intravenously with a slight rise of blood pressure to 90/70 mm. Hg, but again there was a fall and the patient was clinically in shock. At this point mephentermine was given by slow intravenous drip over a period of forty-five minutes, with a rise in blood pressure to 90/60 mm. Hg. Subsequently the blood pressure was maintained at approximately 100 mm. Hg for the next twenty-four hours. However, the patient died suddenly on the second hospital day. Post-mortem examination revealed a massive basilar infarct. The basilar râles noted upon admission persisted throughout the hospital course.

CASE 13.—P. R., an 89-year-old white man, was admitted to the hospital on Aug. 30, 1950, in a state of shock. The patient was completely unresponsive and no history could be obtained. The blood pressure was 75/50 mm. Hg with a heart rate of 85, and electrocardiography showed a recent massive anterior myocardial infarct. Soon after admission the systolic pressure was obtained at 70 mm. Hg and no diastolic could be obtained. The patient was comatose and appeared

in extremis. Mephentermine, 10 mg., was administered intravenously, and the blood pressure rose to 82/60 mm. Hg and then to 90/70 mm. Hg over a period of two hours. At this time the patient began to moan and became somewhat responsive; the blood pressure continued to rise. On the day following admission it was 108/68 mm. Hg, and the patient appeared clinically improved. However, in the next forty-eight hours, there was no urinary output and the patient died suddenly in uremia.

CASE 14.—N. P., an 84-year-old white woman, was admitted to the hospital on Dec. 16, 1950, with a history of sudden onset of severe dyspnea, sweating, and chest pain. She had been known to have had hypertension for many years with repeated episodes of congestive failure. At the time of admission the blood pressure was 175/85 mm. Hg with a heart rate of 124. However, soon after admission the blood pressure had fallen to 98/60 mm. Hg and then continued to fall until the pulse was imperceptible and the patient appeared to be in shock. There were moist râles throughout both lung fields, hepatomegaly, and pedal edema. The patient had been adequately digitalized. Mephentermine, 35 mg., was given intravenously with a prompt response so that within four minutes the blood pressure had risen to 110/70 mm. Hg with a heart rate of 110. An intravenous drip of mephentermine was given for the next hour, maintaining the blood pressure at 112/70 mm. Hg. Within two hours the patient had received a total of 140 mg. of mephentermine with considerable clinical improvement. The patient emerged from the state of shock. However, she became oliguric, and died on the third hospital day in uremia and congestive failure. An autopsy revealed extensive posterior myocardial infarction.

CASE 15.—C. H., a 65-year-old white woman, was admitted to the hospital on April 19, 1950. with a history of substernal pain radiating to the neck and jaw of five hours' duration. At the time of admission the patient appeared to be in extremis. Blood pressure was unobtainable; a thready pulse was detected with a rate of 100. A pericardial friction rub could be heard, and the neck veins were moderately distended. Electrocardiography showed extensive anterior myocardial infarction with right bundle branch block. The patient did not respond to 50 c.c. of 50 per cent glucose and 0.4 Gm. caffeine sodium benzoate. However, ten minutes later she was given mephentermine, 10 mg. intravenously, with a perceptible blood pressure of 65 mm. Hg systolic. This was followed by the intravenous administration of 25 mg. of mephentermine with a rise of blood pressure to 75/50 mm. Hg and a heart rate of approximately 100. The blood pressure was maintained for eight minutes and then again was unobtainable. The administration of 25 mg. of mephentermine was again followed by a transient rise of blood pressure to 80/70 mm. Hg. The administration of 35 mg. of mephentermine intravenously at periodic intervals produced only a transient increase in blood pressure and three hours after admission the patient died in ventricular fibrillation. An autopsy was not obtained.

CASE 16.—M. L., a 71-year-old white woman, was admitted to the hospital on Aug. 15, 1950, with a history of sudden onset of epigastric distress. At the time of admission the blood pressure was 104/78 mm. Hg with a pulse rate of 78. The patient had been previously normotensive. She was cyanotic and there was a cough, pulmonary râles, and the liver was enlarged. Electrocardiogram showed a recent posterior myocardial infarction. On the second hospital day the blood pressure had fallen to 94/72 mm. Hg. The patient became restless and weak, and a friction rub was first heard. The blood pressure gradually continued to decline and on the third hospital day was 84/60 mm. Hg. The pulse was irregular, and there were frequent unifocal ventricular premature beats. Oral quinidine, 0.2 Gm., every six hours was given. On the fourth hospital day the pressure had fallen to 78/58 mm. Hg. The heart rate was 88 and the patient appeared in severe shock. Mephentermine, 35 mg., was given intramuscularly and within ten minutes the pressure had risen to 88/60 mm. Hg, and to 100/78 mm. Hg in twenty minutes. The pressure remained approximately at this level for the next twelve hours. The patient's color and pulse improved as the blood pressure rose. On the evening of the fourth hospital day the patient suddenly began to gasp for breath and died within five minutes. An autopsy was not obtained.

CASE 17.—J. K., a 78-year-old white man, was admitted to the hospital on Aug. 14, 1949, with a history of sudden pain in the chest and radiation to both arms and lower jaw. There was a history of moderate diabetes for twenty-eight years. The patient had been normotensive, and had no history of congestive failure. On admission the patient appeared acutely ill. The blood

pressure was 150/90 mm. Hg with a heart rate of 84. The electrocardiogram showed a recent massive anterolateral myocardial infarction. The patient appeared to be doing well during the first hospital day. On the second hospital day the patient had sudden intense precordial pain. The blood pressure fell to 80/50 mm. Hg and the pulse became imperceptible; 50 c.c. of 50 per cent glucose were given intravenously without effect. The patient remained in a hypotensive state for three hours without response to oxygen and caffeine. Repeated doses of mephentermine, 5, 10, and 25 mg., were given intravenously over a period of forty-five minutes with only a transient elevation of the blood pressure from unobtainable values to approximately 70 mm. Hg systolic. The patient died without emerging from shock. An autopsy was not obtained.

CASE 18.—(Fig. 3) A. L., a 52-year-old white man, was admitted to the hospital on July 13, 1950. He had been admitted to the hospital for evaluation of his coronary insufficiency in anticipation of a possible surgical interference. At the time of admission the blood pressure was 120/80 mm. Hg with a heart rate of 95, and there was no evidence of congestive failure. On the day following admission, approximately four hours after Priodax had been given orally, he developed diarrhea, nausea, and vomiting, and suddenly experienced severe chest pain. The blood pressure was found to be 60 mm. Hg systolic, the diastolic pressure being unobtainable. The patient was in clinical shock; the pulse was weak and thready. Oxygen was given by a face mask. The pulse was barely perceptible for a period of one hour at which time mephentermine, 7 mg., was given intravenously and a systolic pressure of 60 mm. Hg could be obtained. Mephentermine, 14 mg., was then given intravenously with little change in the blood pressure. An electrocardiogram showed evidence of recent posterior myocardial infarction and severe myocardial ischemia. A total of 105 mg. of mephentermine was given intravenously with a gradual rise of blood pressure to 110/80 mm. Hg with a heart rate of 125. As the blood pressure rose the chest pain, of which the patient had bitterly complained, gradually diminished. The patient became alert and appeared to be over the crisis. However, one hour after the patient had emerged from the shock state he suddenly died. An autopsy was not performed.

REFERENCES

1. Master, A. M., Jaffe, H. L., Dack, S., and Silver, N.: The Course of the Blood Pressure Before, During, and After Coronary Occlusion, AM. HEART J. **26**:91, 1943.
2. Mintz, S. S., and Katz, L. N.: Recent Myocardial Infarction, Arch. Int. Med. **80**:205, 1947.
3. Epstein, F. H., and Relman, A. S.: Transfusion Treatment of Shock Due to Myocardial Infarction, New England J. Med. **241**:889, 1949.
4. Stewart, H. J.: *Quoted in* Conferences on Therapy. Treatment of Coronary Artery Disease, Am. J. Med. **1**:291, 1946.
5. Gilbert, N. C.: Treatment of Coronary Thrombosis, M. Clin. North America **28**:1, 1944.
6. Master, A. M., Jaffe, H. L., Dack, S., and Grishman, A.: Coronary Occlusion, Coronary Insufficiency, and Angina Pectoris, AM. HEART J. **27**:803, 1944.
7. Sampson, J. J., and Singer, I. M.: Plasma and Blood Infusion Following Myocardial Infarction, AM. HEART J. **38**:54, 1949.
8. Corday, E., Bergman, H. D., Schwartz, L. L., Sprintzler, R. J., and Prinzmetal, M.: Studies on the Coronary Circulation. IV. The Effect of Shock on the Heart and Its Treatment, AM. HEART J. **37**:560, 1949.
9. Schwartz, W. B.: The Treatment of Shock Accompanying Myocardial Infarction, AM. HEART J. **33**:169, 1947.
10. Brofman, B. L., Hellerstein, H. K., and Caskey, W. H.: Mephentermine—An Effective Pressor Amine. Clinical and Laboratory Observations, AM. HEART J. **44**:395, 1952.
11. Wright, I. S., Marple, C. D., and Beck, D. F.: The Use of Anticoagulants in the Treatment of Myocardial Infarction, Mod. Concepts Cardiovas. Dis. **18**:55, 1949.
12. Rosenbaum, F. F., and Levine, S. A.: Prognostic Value of Various Clinical and Electrocardiographic Features of Acute Myocardial Infarction: Immediate Prognosis, Arch. Int. Med. **68**:913, 1941.
13. Hellerstein, H. K., and Brofman, B. L.: The Treatment of the Hypotensive State Accompanying Myocardial Infarction, Mod. Concepts Cardiovas. Dis. **20**:8, 1951.
14. Orias, O.: Dynamic Changes in Ventricles Following Ligation of Ramus Descendens Anterior, Am. J. Physiol. **100**:629, 1932.
15. Tennent, R., and Wiggers, C. J.: Effect of Coronary Occlusion on Myocardial Contraction, Am. J. Physiol. **112**:351, 1935.

16. Pritchard, W. H., Hellerstein, H. K., Lewis, R., and Inkley, S.: A Preliminary Report on the Study of Myocardial Infarction by Auricular Catheterization, J. Lab. & Clin. Med. **34**:1737, 1949.
17. Grishman, A., and Master, A. M.: Cardiac Output in Coronary Occlusion Studied by the Wezler-Boger Physical Method, Proc. Soc. Exper. Biol. & Med. **48**:207, 1941.
18. Wiggers, C. J.: Myocardial Depression in Shock; a Summary of Cardiodynamic Studies, AM. HEART J. **33**:533, 1947.
19. Master, A. M., Dack, S., Ham, H., Freedman, D., and Fields, L. E.: Acute Coronary Insufficiency Due to Hemorrhage, Circulation **1**:1302, 1950.
20. Dack, S., Corday, E., and Master, A. M.: The Heart in Acute Hemorrhage: A Clinical and Electrocardiographic Study, AM. HEART J. **42**:161, 1951.
21. Fishberg, A. M., Hitzig, W. M., and King, F. H.: Circulatory Dynamics in Myocardial Infarction, Arch. Int. Med. **54**:997, 1934.
22. Boyer, N. H.: Cardiogenic Shock, New England J. Med. **230**:226, 256, 1944.
23. Kupfer, S.: Can Experimental Shock be Induced by Coronary Occlusion, Proc. Soc. Exper. Biol. & Med. **76**:134, 1951.
24. Massie, E., and Miller, W. C.: The Heart Size and Pulmonary Findings During Acute Coronary Thrombosis, Am. J. M. Sc. **206**:353, 1943.
25. Stead, E. A., Jr., and Ebert, R. V.: Shock Syndrome Produced by Failure of the Heart, Arch. Int. Med. **69**:369, 1942.
26. Gollwitzer-Meier, K., and Kruger, E.: Einflusz der Herznerven auf den Gaswechsel des Warmbluterherzens, Pflüger's Arch. f. d. ges. Physiol. **240**:89, 1938.
27. Eckstein, R. W., Stroud, M. III, Eckel, R., Dowling, C. V., and Pritchard, W. H.: Effects of Control of Cardiac Work Upon Coronary Flow and 0_2 Consumption After Sympathetic Nerve Stimulation, Am. J. Physiol. **163**:539, 1950.
28. Silber, E. N., Levin, B. D., Becker, G. H., and Levy, R. C.: Treatment of Shock in Recent Myocardial Infarction by Intra-arterial Transfusion, J. A. M. A. **147**:1626, 1951.
29. Nouse, D. C., and Lyons, R. H.: Personal communication.
30. Bing, R. J., Maraist, F. M., Damann, J. F., Draper, A., Heimbecker, R., Daley, R.,Gerard, R., and Colazel, P.: Effect of Strophanthin on Coronary Blood Flow and Cardiac Oxygen Consumption of Normal and Failing Human Hearts, Circulation **2**:513, 1950.
31. Wegria, R., Geyer, J. H., and Brown, B. C.: Fibrillation Threshold After Administration of Digitalis and Ouabain, J. Pharmacol. & Exper. Therap. **71**:336, 1941.
32. Gilbert, R. P., Anderson, L., Aldrich, S. L., and Goldberg, M. A.: Further Studies on Cardiac Output in Acute Infarction, J. Lab. & Clin. Med. **38**:813, 1951.
33. Berman, E. F., and Akman, L. C.: Intra-arterial Infusion in the Treatment of Shock Resulting From Coronary Occlusion, AM. HEART J. **43**:264, 1952.

CARDIAC ARRHYTHMIAS FOLLOWING THE USE OF LARGE DOSES OF CENTRAL NERVOUS SYSTEM STIMULANTS

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ALTHOUGH caffeine, nikethamide, and amphetamine are commonly employed to combat central nervous system depression, relatively little attention has been directed to the development of cardiac arrhythmias associated with the use of large doses of these drugs. It is the purpose of this communication, by describing two illustrative cases, to call attention to such arrhythmias as a possible complication of the administration of massive doses of these stimulants.

CASE REPORTS

CASE 1.—A 19-year-old white woman was admitted in coma after taking an overdose of morphine sulfate. Examination showed cyanosis, no discernible respiratory movements, a regular pulse of 122 per minute, and blood pressure of 104/70 mm. Hg. In conjunction with other measures such as positive pressure oxygen inhalation, she received 12 Gm. of nikethamide, 14 Gm. of caffeine, and sodium benzoate, and 40 mg. of amphetamine intravenously during the first six hours of treatment. At this time because spontaneous respiration had been restored and the patient was beginning to regain consciousness, emergency treatment was discontinued. The patient was then given 0.5 Gm. caffeine sodium benzoate intramuscularly at three-hour intervals for the next twenty-four hours. Approximately fifteen hours after admission, a coupled rhythm was detected and an electrocardiogram showed bigeminy due to ventricular premature contractions (Fig. 1,*A*). Twenty-four hours after caffeine was discontinued, sinus rhythm was restored. The electrocardiogram at this time showed prominent U waves at the site of the previous ventricular beats (Fig. 1,*B*). By the fourth hospital day, the electrocardiogram had reverted to normal (Fig. 1,*C*). At no time during her course was there any hypotension or shock-like state.

CASE 2.—A 56-year-old white woman was admitted in coma about three hours after ingestion of an undetermined number of capsules containing 0.1 Gm. of Seconal each. She was completely unresponsive; pulse was regular at 90 per minute, respirations 12 per minute, and blood pressure 116/70 mm. Hg. The pupils reacted sluggishly to light; the corneal and deep tendon reflexes were absent. Within the first five hours she was given 11 Gm. of nikethamide, 11.5 Gm. of caffeine sodium benzoate, and 100 mg. of amphetamine intravenously. She remained areflexic and unresponsive; because of a drop in blood pressure to 90/50 mm. Hg, all medication was discontinued and an electrocardiogram was made. This showed depression of S-T segments and large U waves (Fig. 2,*A*). Rhythm soon became irregular due to the appearance of ventricular premature beats (Fig. 2,*B*) and rapidly progressed to chaotic heart action (Fig. 2,*C*). Cardiac arrest occurred three hours later, despite treatment with procaine amide, calcium gluconate, and epinephrine.

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DISCUSSION

Nikethamide, caffeine, and amphetamine are all said to stimulate the myocardium directly,[1] but serious cardiac arrhythmias during therapy with these drugs have not been described frequently.

We have found no record of arrhythmias with nikethamide alone. Caffeine, of course, is often blamed for the production of extrasystoles and the omission of coffee is usually recommended in patients who complain of pulse irregularities.[2,3] On two occasions, we have given caffeine sodium benzoate intravenously to human beings in doses of 1 Gm. at ten-minute intervals to a total of 6 Gm. without any effect on the electrocardiogram other than an increase in rate.

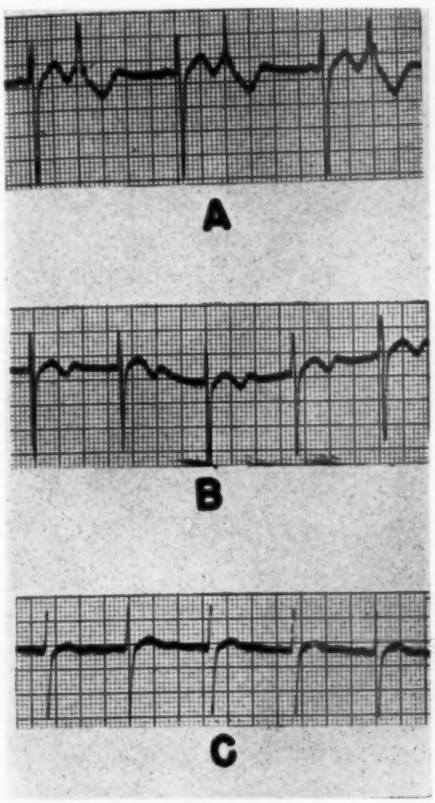

Fig. 1.—Electrocardiograms in Case 1.

There are several references to the production of arrhythmias by amphetamine. Anderson and Scott[4] observed circulatory collapse with 4:1 heart block and extrasystoles in one patient after 30 mg. of amphetamine by mouth. Apfelberg[5] reported circulatory collapse and coma after 140 mg. by mouth, but an electrocardiogram was not taken until after recovery and was normal. Waud[6] described paroxysmal tachycardia and numerous extrasystoles for several days on two occasions in a young man after prolonged inhalation of amphetamine. Ehrich and his associates[7] found bradycardia followed by tachycardia of 300 to 350 per minute in rabbits given large doses of amphetamine.

A recent case report of Dilantin poisoning[8] is of interest. The patient, over a period of forty hours, received 2.88 Gm. of amphetamine, 144 Gm. of nikethamide, and 72 Gm. of caffeine intravenously. After about twenty-four hours, a bizarre arrhythmia consisting of rapid auricular fibrillation with paroxysms of bifocal ventricular tachycardia developed.

The electrocardiographic events in the two cases described above were similar. In the first case, when the use of stimulants was discontinued, bigeminy due to ventricular premature contractions gave way to a normal sinus rhythm but prominent U waves were visible at the sites where the ventricular beats had been

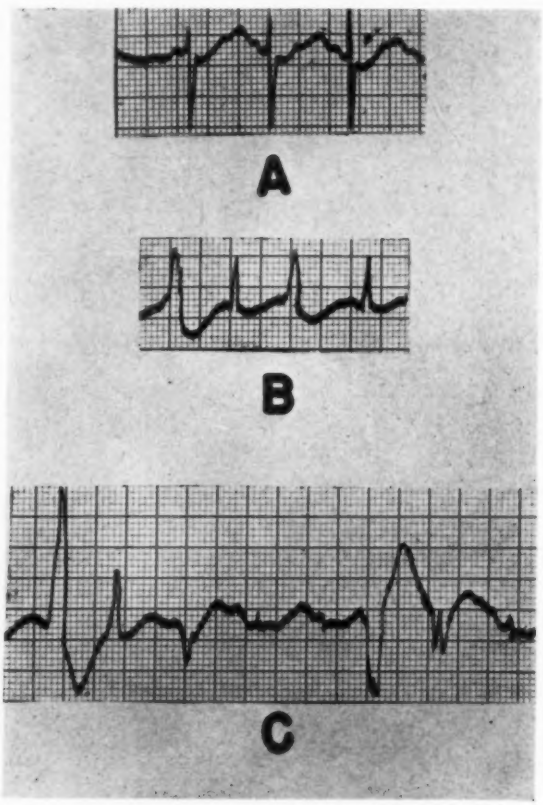

Fig. 2.—Electrocardiograms in Case 2.

present. In the second case, the first tracing showed large U waves; later, ventricular premature beats replaced the U waves and as the disturbance progressed, heart action became chaotic. If the U wave be accepted as representing the so-called supernormal period of ventricular irritability as described by Nahum and Hoff,[9] one might postulate that the sequence of events in these two patients was one of increasing myocardial irritability.

It is not possible to state which of the drugs, singly or in combination, was responsible for the cardiac disturbance in these patients. We have found no record of such arrhythmias due to morphine or barbiturate poisoning alone and the onset of the disturbance of rhythm after treatment is evidence against this possibility.

SUMMARY AND CONCLUSIONS

Two cases of cardiac arrhythmias in patients treated with large doses of nikethamide, caffeine, and amphetamine are reported and it is suggested on the basis of electrocardiographic changes that an increase in the ventricular supernormal period was the basic disorder. Although pertinent published data are few, the possibility of serious disturbances of cardiac rhythm should be borne in mind when central nervous system stimulants are used.

REFERENCES

1. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, 1941, The Macmillan Company, pp. 271, 277, 439.
2. White, P. D.: Heart Disease, ed. 4, New York, 1951, The Macmillan Company, p. 871.
3. Friedberg, C. K.: Diseases of the Heart, Philadelphia, 1949, W. B. Saunders Company, pp. 254, 257.
4. Anderson, E. W., and Scott, W. C. M.: Cardiovascular Effects of Benzedrine, Lancet **2**:1461-1462, 1936.
5. Apfelberg, B.: A Case of Benzedrine Sulfate Poisoning, J. A. M. A. **110**:575-576, 1938.
6. Waud, S. P.: The Effects of Toxic Doses of Benzyl Methyl Carbinamine (Benzedrine) in Man, J. A. M. A. **110**:205-207, 1938.
7. Ehrich, W. E., Lewy, F. H., and Krumbhaar, E. B.: Experimental Studies Upon the Toxicity of Benzedrine Sulfate in Various Animals, Am. J. M. Sc. **198**:785-803, 1939.
8. Tichner, J. B., and Enselberg, C. D.: Suicidal Dilantin (Sodium Diphenylhydantoin) Poisoning, New England J. Med. **245**:723-725, 1951.
9. Nahum, L. H., and Hoff, H. E.: The Interpretation of the U Wave of the Electrocardiogram, Am. Heart J. **17**:585-598, 1939.

THE ACTION OF PROCAINE AMIDE IN COMPLETE HEART BLOCK

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IT IS now well recognized that ventricular standstill is not the sole mechanism of the syncopal attacks of heart block. It has been demonstrated by several observers[1-8] that the attacks are frequently due to varying degrees of ventricular acceleration including ventricular fibrillation. Schwartz and his associates[4] in a series of reports have carried out a detailed analysis of the graphic records preceding, during and following the Adams-Stokes seizures associated with ventricular fibrillation. Parkinson, Papp, and Evans[5] reported an electrocardiographic analysis of sixty-four syncopal attacks in heart block. Ventricular acceleration and fibrillation were the mechanisms in thirty-one instances.

It has been shown in earlier studies that epinephrine and many related compounds are effective in the therapy of ventricular standstill.[9,10] However, there is no effective drug for the prevention of ventricular acceleration and fibrillation in heart block. Reports indicate that quinidine is not only ineffective for this purpose but that the drug may precipitate ectopic ventricular rhythms and increase the frequency and duration of the seizures. De Boer[2] reported that quinidine was ineffective in the prevention of ventricular fibrillation in heart block and concluded that the drug actually induced this arrhythmia. A patient with complete heart block in whom attacks of ventricular fibrillation occurred during the course of quinidine therapy has been described by Kerr and Bender.[1] Davis and Sprague[3] discussed the mechanism of ventricular fibrillation in heart block and reported a patient in whom attacks recurred while on quinidine therapy. Schwartz and Jezer[11] administered quinine and quinidine to two patients with complete heart block who were subject to paroxysms of ventricular fibrillation. Both drugs in small doses by vein consistently induced a prefibrillatory mechanism or transient periods of ventricular fibrillation.

Procaine amide (Pronestyl) has recently been introduced in the therapy of cardiac arrhythmias.[12-18] The drug is especially effective in the treatment of ectopic beats and rhythms arising in the ventricles. In a previous report,[15] it was suggested that procaine amide might be indicated for the prevention of paroxysms of ventricular acceleration and fibrillation in complete heart block. It has been shown that procaine amide has a quinidine-like action on the heart.[19] Since quinidine appears to induce ectopic ventricular rhythms in heart block, the pres-

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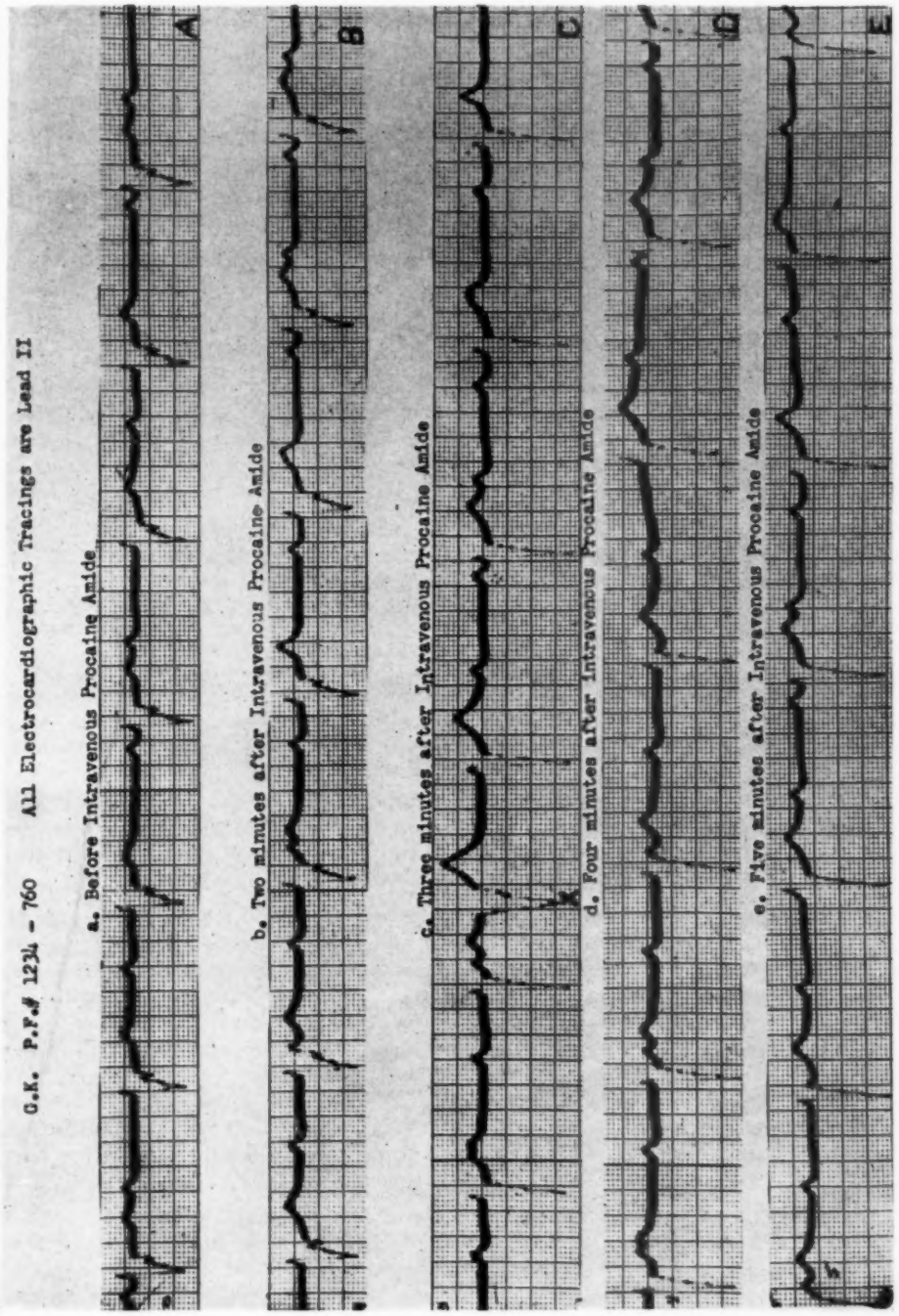
G.K. P.F.# 1234 - 760 All Electrocardiographic Tracings are Lead II
a. Before Intravenous Procaine Amide
b. Two minutes after Intravenous Procaine Amide
c. Three minutes after Intravenous Procaine Amide
d. Four minutes after Intravenous Procaine Amide
e. Five minutes after Intravenous Procaine Amide
A
B
C
D
E

Fig. 1.—Patient G. K. Slowing of the ventricular rate and the appearance of a ventricular extrasystole following the administration of 500 mg. of procaine amide (details in text).

ent study was carried out to determine the action of procaine amide in this condition.

Procaine amide was administered intravenously to four patients with complete heart block with continuous recording of the electrocardiogram. At the outset the drug was to be injected in a dose of 500 mg. at a rate of 200 mg. per minute. This was the procedure employed in our previous study.[15] However, it was apparent in our observation in Case 2 that the drug could produce pronounced effects in heart block in relatively small doses and the dose was reduced to 150 and 200 mg. The drug was injected at a slow rate and was discontinued when there was a slowing of the ventricular rate and the appearance of ectopic ventricular activity.

CASE REPORTS

CASE 1.—G.K., a 76-year-old retired salesman, entered the hospital with the following complaints: dysuria, nocturia, and acute urinary retention. He was a known hypertensive, was on digitalis, and he had received mercurial diuretics for edema of the extremities. On physical examination, the heart rate were 45 per minute, a Grade I systolic apical murmur and moderate cardiac enlargement were demonstrated. The blood pressure was 170 mm. Hg systolic and 70 diastolic.

In Fig. 1, strip *A* shows complete heart block with a ventricular rate of 45 per minute. Lower strips were taken after an intravenous injection of 500 mg. of procaine amide. Strip *C*, taken three minutes after the start of the injection, shows a ventricular rate of 36, and an occasional ventricular ectopic beat (*X*). The ventricular rate remains at 36 in strips *D* and *E* taken one and two minutes after strip *C*.

CASE 2.—E.M. was a 62-year-old man, a retired carpenter. He suffered an attack of acute rheumatic fever at the age of 18 at which time a diagnosis of heart disease was made. He suffered a second attack of rheumatic fever at the age of 34. On admission to the hospital, his complaints were dyspnea, expectoration of bloody sputum, and edema of the ankles. On physical examination, murmurs indicative of both mitral and aortic valvular disease were present. The heart rate was 34 per minute and the blood pressure was 140 mm. Hg systolic and 80 diastolic. The diagnoses were: rheumatic heart disease, aortic and mitral valvular disease, congestive failure, and complete heart block.

In Fig. 2, strip *A* shows complete heart block, ventricular rate 34 per minute. Strips *B* and *C* taken two and three minutes after the start of an intravenous injection of 200 mg. of procaine amide show a reduction of the ventricular rate to 25 and 20 beats per minute. The injection was discontinued at this time. Strips *D* and *E* taken four and four and one-half minutes after the start of the injection show long periods between basic ventricular complexes and many multifocal ectopic ventricular beats. Strips *F* and *G* taken five and six and one-half minutes after the start of the procedure show long periods of ventricular arrest and aberrant ventricular complexes. Strips *H*, *I*, and *J* taken nine, ten, and fifteen minutes after the start of the injection show heart block with multifocal ventricular beats. This type of reaction continued to thirty minutes after the start of the experiment when there was a return to the complete heart block pattern which was present prior to the administration of the drug (strip *K*).

CASE 3.—F.H., a 67-year-old retired contractor, entered the hospital with symptoms of shortness of breath and edema of the ankles, which had been present intermittently for three years. There was a history of a previous digitalization with a reduction of heart rate to 20 per minute. He was known to have had a hypertension of 200 mm. Hg systolic or more for several years and he had received mercurial diuretics periodically. On physical examination, the patient was dyspneic and orthopneic. The heart was greatly enlarged and there was a systolic apical murmur present. The heart rate was 34 and the blood pressure was 170 mm. Hg systolic and 80

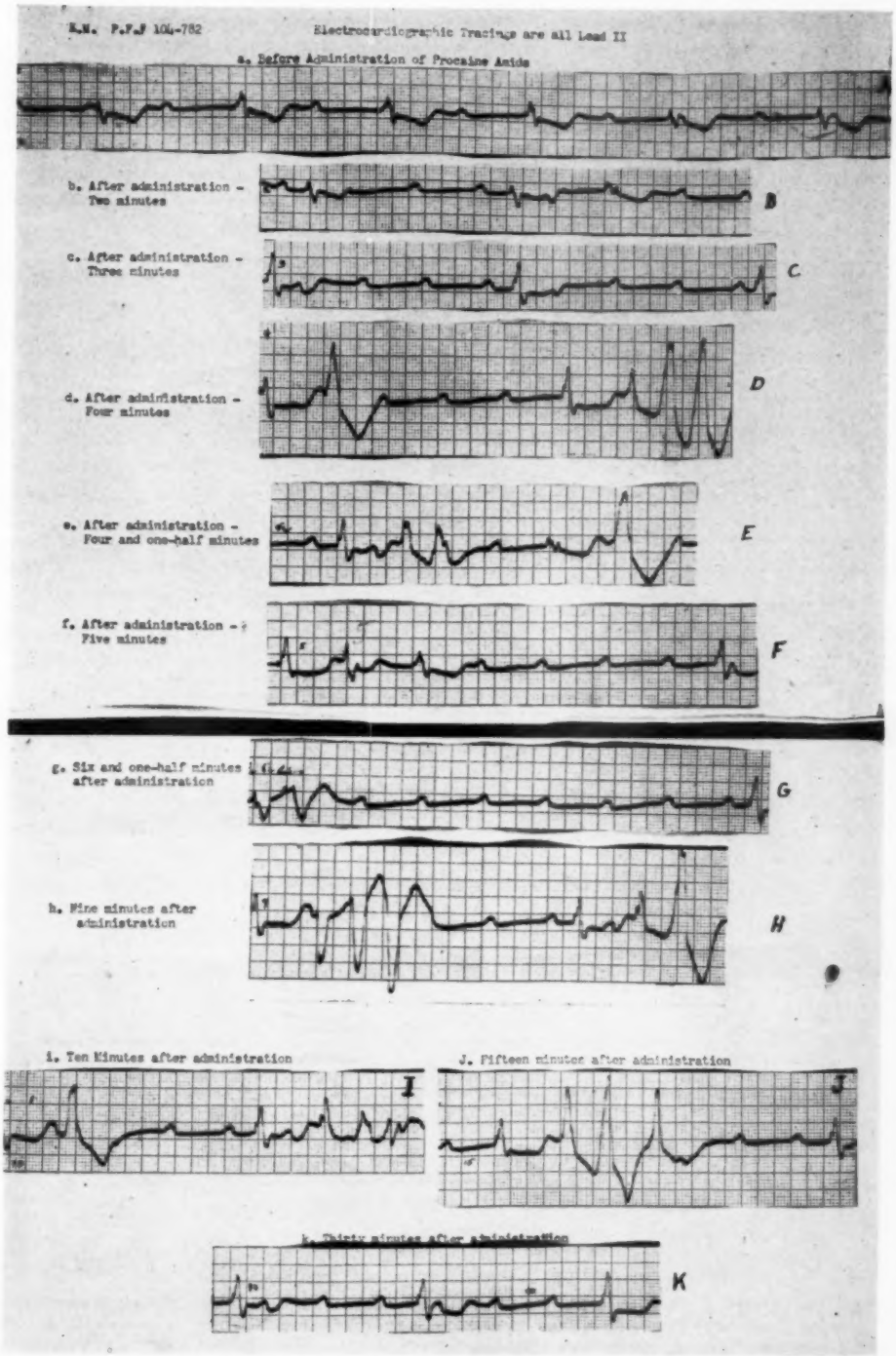

Fig. 2.—Patient E. M. Slowing of the ventricular rate and the appearance of many multifocal ectopic beats after the intravenous injection of 200 mg. of procaine amide (details in text).

diastolic. There were moist râles heard throughout both lung fields. The diagnoses were: hypertensive heart disease, congestive failure, auricular fibrillation, and complete heart block.

In Fig. 3, strip *A* shows auricular fibrillation, complete heart block with a ventricular rate of 34 per minute. Strip *C* taken three minutes after the start of an injection of 200 mg. of procaine amide shows a ventricular rate of 20 per minute and the drug was discontinued. Strips *D*, *E*, *F*, *G*, *H*, and *I*, taken at intervals of one minute, show increasing intervals between basic ventricular complexes. The basic complexes are largely replaced by multifocal ectopic ventricular beats. Strips *J* and *K*, taken ten and fifteen minutes after the start of the procedure, show a return to the original ventricular rate and a disappearance of the ectopic beats.

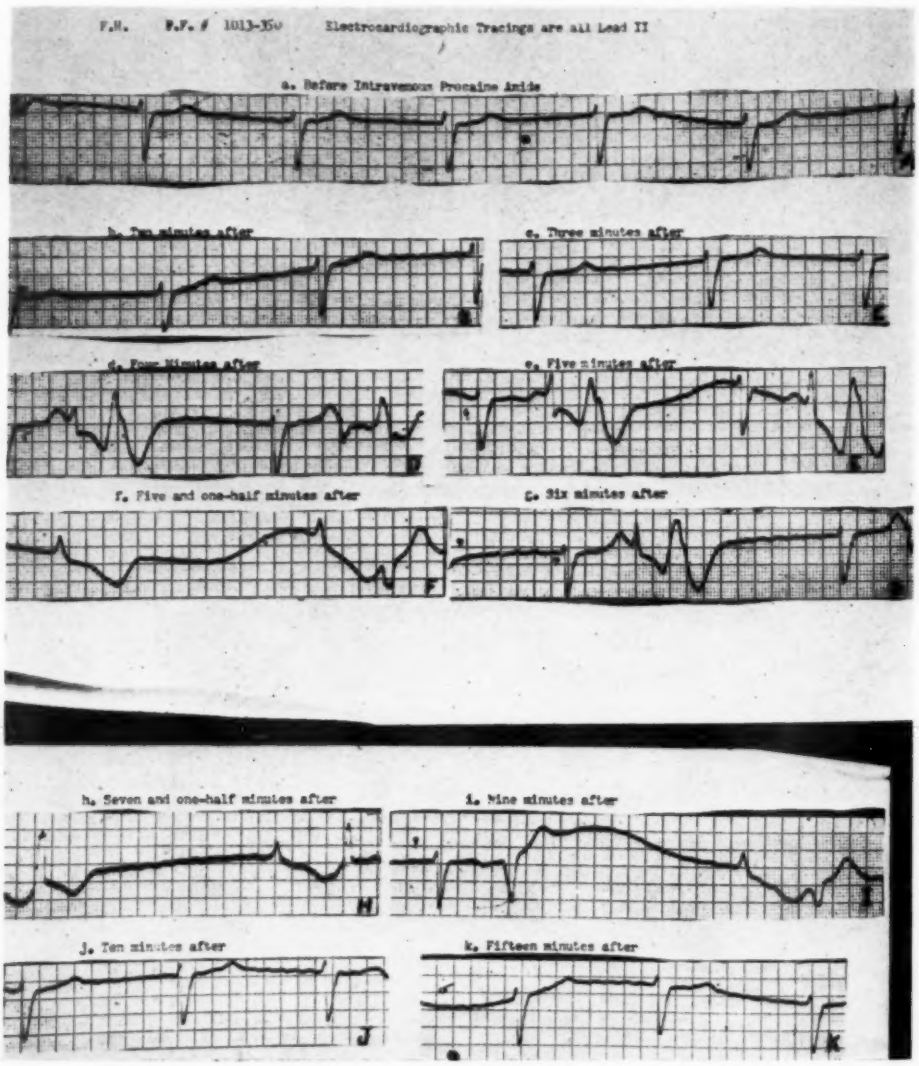
F.H. H.F. # 1013-35 Electrocardiographic Tracings are all Lead II
a. Before Intravenous Procaine Amide
b. Two minutes after
c. Three minutes after
d. Four minutes after
e. Five minutes after
f. Five and one-half minutes after
g. Six minutes after
h. Seven and one-half minutes after
i. Nine minutes after
j. Ten minutes after
k. Fifteen minutes after

Fig. 3.—Patient F. H. Auricular fibrillation and complete heart block showing a reduction of the ventricular rate and the development of multifocal ectopic ventricular activity following an intravenous injection of 200 mg. of procaine amide (details in text).

CASE 4.—W.C., an 83-year-old man, was admitted to the hospital because of dyspnea and increasing edema of the lower extremities. The heart was dilated and a blowing systolic apical murmur was present. The heart rate was 40 per minute and the rhythm was regular. The blood

pressure was 270 mm. Hg systolic and 110 mm. Hg diastolic. The diagnoses were: hypertensive heart disease, congestive heart failure, and complete heart block.

In Fig. 4, strip *A* shows complete heart block and a ventricular rate of 40 per minute. After the administration of 150 mg. of procaine amide by vein the ventricular rate was reduced to 32, (strip *C* taken four minutes after the start of the injection). In the first portion of strip *D*, taken thirty seconds later, multifocal ventricular beats appear followed by a paroxysm of ventricular fibrillation. This paroxysm continued for 2.2 minutes (strips *E*, *F*, and *G*). This was followed by a period of ventricular standstill shown at end of strip *G* and continuing for 27 seconds (Fig. 5,*H*.). There was a gradual return of ventricular complexes (strips *I*, *J*, and *K*) at a slow rate interrupted by a short period of nodal tachycardia (strip *L*). Strip *M*, taken thirteen minutes after the injection of the procaine amide, shows reappearance of complete heart block with alternating types of ventricular complexes. Strips *N* and *O* taken fifteen and thirty minutes after the injection of the drug show a return to the pre-injection pattern.

A fifth patient was studied in whom ventricular fibrillation was demonstrated as the mechanism of frequent syncopal attacks (Fig. 6). In the interval between attacks, the electrocardiogram frequently showed short runs of ventricular oscillations. She was known to have had hypertension for several years and she had been admitted to the hospital eighteen months before, at which time complete heart block was present. On physical examination a moderate cardiac enlargement and a blowing systolic apical murmur were present. The heart rate ranged from 24 to 32 per minute. The duration of the syncopal attacks varied from fifteen seconds to three minutes. At the onset of an attack, she became apneic, her face became very pale, and she became rapidly irresponsive. Observing the electrocardiogram in a seizure, it was noted that consciousness and normal respiration returned promptly with the cessation of the ventricular fibrillation. In Fig. 6, strip *A* taken during a syncopal attack shows a paroxysm of ventricular fibrillation. Strip *B*, taken between seizures, shows short runs of aberrant ventricular oscillations interrupting periods of complete block. Schwartz, from his extensive studies on transient ventricular fibrillation in man, concluded that these recurring runs of ventricular irregularities are the initial fibrillary periods of the ventricle and they invariably foreshadow the appearance of longer seizures. Since the intravenous injection of procaine amide, from previous observations,[12-18] consistently and promptly abolished ectopic ventricular rhythms, the drug was administered to this patient at a time when the short runs of ventricular oscillations were present. Fig. 6,*B* was taken before the injection of the drug. A dose of 500 mg. of procaine amide was injected by vein and a continuous electrocardiogram was made for five minutes and thereafter at five-minute intervals for a period of thirty minutes. Fig. 6,*C*, taken ten minutes after the administration of the drug, is typical of a strip of the electrocardiogram during this period and it shows a persistence of the ectopic ventricular activity. During the course of the hospital stay, procaine amide, administered orally in doses of 500 mg. every four hours, had no effect on the attacks of ventricular fibrillation.

DISCUSSION

In each of the first four patients, the administration of procaine amide was followed by a reduction in the ventricular rate. In two instances, multifocal ectopic ventricular beats appeared and in one patient a transient ventricular fibrillation occurred. In the fifth patient, in whom short runs of ventricular acceleration were present, procaine amide showed no tendency to eliminate these ectopic rhythms. This is in contrast to the consistent action of this drug in abolishing ectopic ventricular beats in the absence of heart block. The tendency for antifibrillatory drugs, including quinidine, to induce ectopic ventricular rhythms and fibrillation is well known.[1-3,11,20-23] This action is especially striking in the case of alpha fagarine, a potent antifibrillatory drug, and related compounds. Scherf and associates[23] reported that following the administration of alpha fagarine, sinus rhythm was frequently restored in auricular flutter and fibrillation. However, of the thirteen cases, seven exhibited multifocal ventricu-

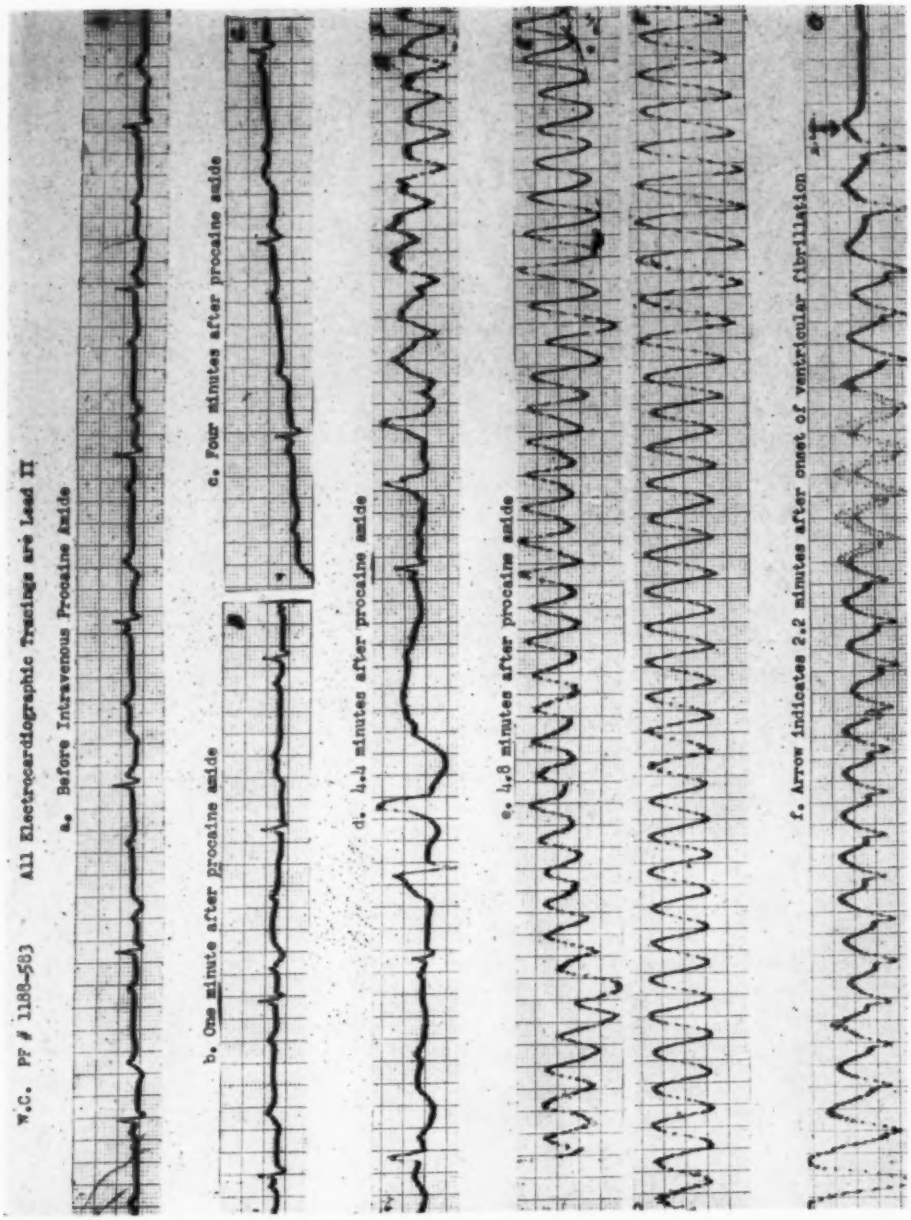
W.C. PF # 1188-563 All Electrocardiographic Tracings are Lead II
a. Before Intravenous Procaine Amide
b. One minute after procaine amide
c. Four minutes after procaine amide
d. 4.4 minutes after procaine amide
e. 4.8 minutes after procaine amide
f. Arrow indicates 2.2 minutes after onset of ventricular fibrillation

Fig. 4.—Patient W. C. Reduction in the ventricular rate and the development of a paroxysm of ventricular fibrillation following the intravenous administration of 150 mg. of procaine amide (details in text).

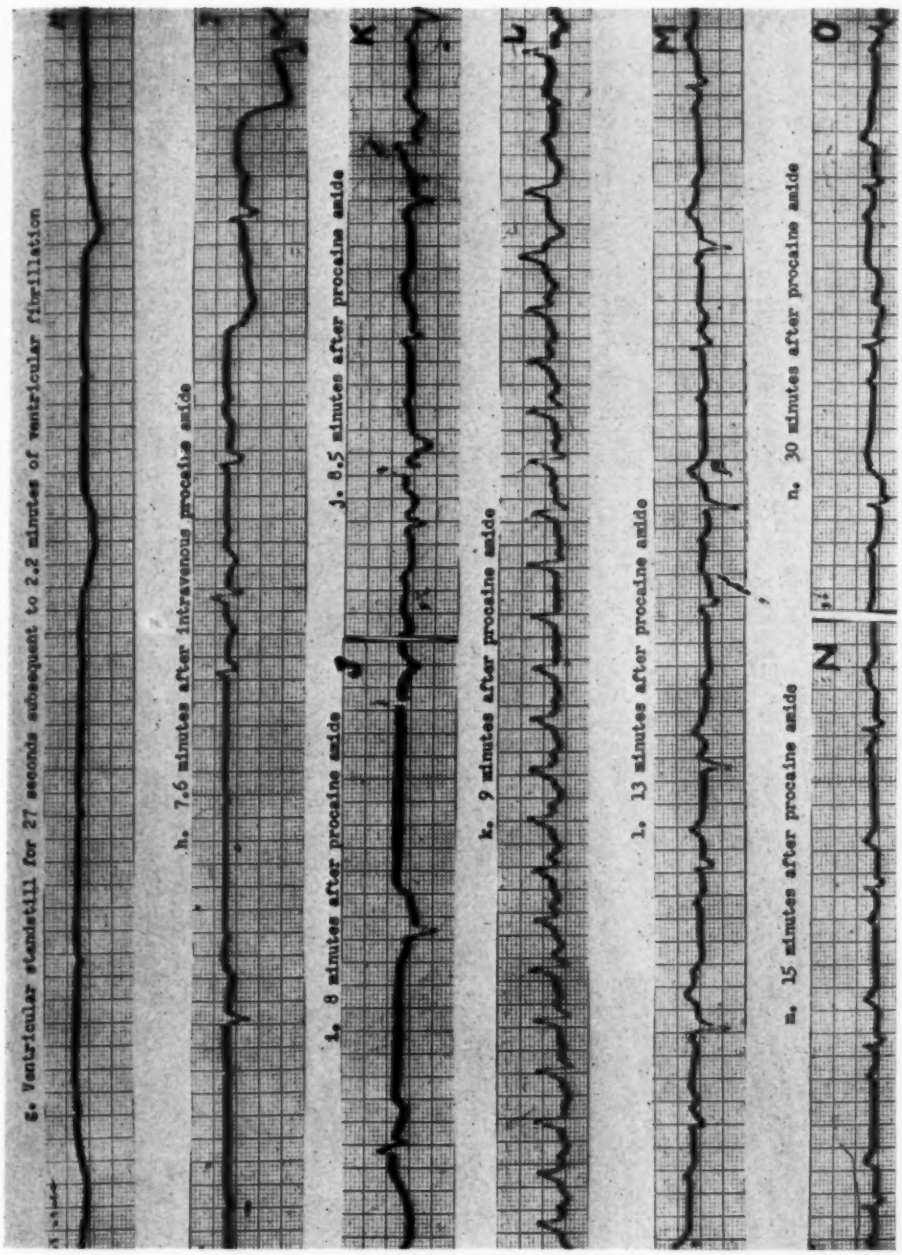
g. Ventricular standstill for 27 seconds subsequent to 2.2 minutes of ventricular fibrillation
h. 7.6 minutes after intravenous procaine amide
i. 8 minutes after procaine amide
j. 8.5 minutes after procaine amide
k. 9 minutes after procaine amide
l. 13 minutes after procaine amide
m. 15 minutes after procaine amide
n. 30 minutes after procaine amide

Fig. 5.—Continuation of Fig. 4. Period of ventricular standstill following the ventricular fibrillation shown in Fig. 4. This is followed by a gradual appearance of ventricular complexes at an increasing rate and finally a return to the pre-injection pattern of complete heart block (details in text).

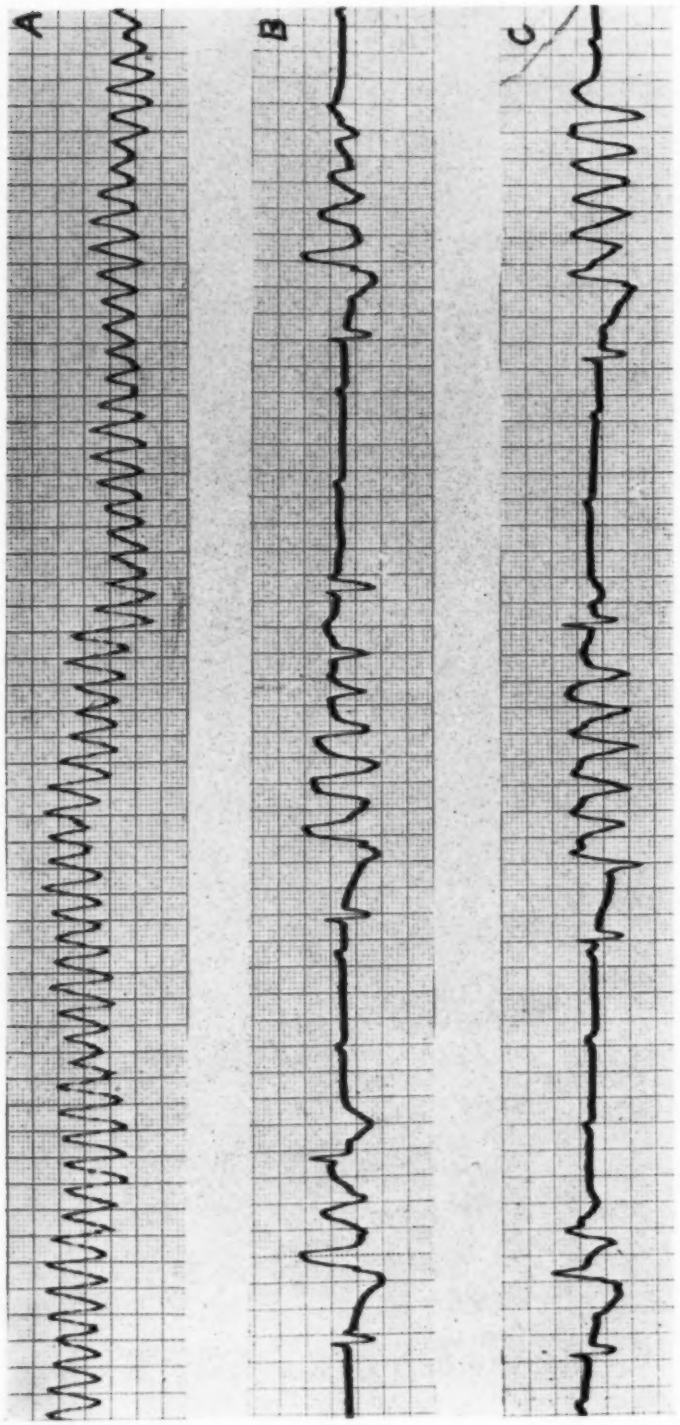

Fig. 6.—Patient S. S. Strip *A*, Ventricular fibrillation during a seizure; strip *B*, short runs of ectopic ventricular rhythm, and strip *C*, persistence of the runs of ectopic ventricular rhythm after the administration of procaine amide 500 mg.

lar beats after sinus rhythm was established and in two cases fatal ventricular fibrillation occurred. We have also noted the appearance of multifocal ectopic ventricular beats following the administration of alpha fagarine.[24] During our studies on procaine amide in arrhythmias,[15] we examined our records carefully for evidence of induced ectopic beats or rhythms from new foci, and observed no such effect. However, it appears from the present study that procaine amide, like quinidine, in complete heart block disposes to ectopic ventricular rhythms including fibrillation. It would seem that in the presence of conduction defect, the administration of the drug may be hazardous.

SUMMARY AND CONCLUSIONS

In four patients with complete heart block, the intravenous administration of procaine amide was followed by a definite reduction in the ventricular rate.

In two patients, frequent multifocal ventricular beats appeared, and in a third patient, there occurred a paroxysm of ventricular fibrillation followed by a period of ventricular standstill.

In a patient with complete block, frequent attacks of ventricular fibrillation were present; procaine amide had no effect on the attacks and the drug did not eliminate short runs of aberrant ventricular oscillations which occurred between major attacks.

These observations indicate that the administration of procaine amide is ineffective and may be hazardous in complete heart block.

REFERENCES

1. Kerr, W. J., and Bender, W. L.: Paroxysmal Ventricular Fibrillation With Cardiac Recovery in a Case of Auricular Fibrillation and Complete Heart Block While Under Quinidine Therapy, Heart **9**:269, 1922.
2. De Boer, S.: Ventricular Fibrillation in Total Heart Block and the Action of Quinidine and Quinine Preparations in Heart Block, Nederl. tijdschr. v. geneesk. **2**:2617, 1926.
3. Davis, D., and Sprague, B.: Ventricular Fibrillation: Its Relation to Heart Block, Am. Heart J. **4**:559, 1929.
4. Schwartz, S. P.: Transient Ventricular Fibrillation, Arch. Int. Med. **49**:282, 1932.
5. Gertz, G., Kaplan, H. O., Kaplan, L., and Weinstein, W.: Cardiac Syncope Due to Paroxysms of Ventricular Flutter, Fibrillation and Asystole in a Patient With Varying Degrees of A-V Block and Intraventricular Block, Am. Heart J. **16**:225, 1938.
6. Parkinson, J., Papp, C., and Evans, W.: The Electrocardiogram of the Stokes-Adams Attack, Brit. Heart J. **3**:171, 1946.
7. Parsonnet, A. E., Berstein, A., and Klosk, E.: Ventricular Fibrillation With Special Reference to the Morgagni-Adams-Stokes Syndrome: Report of an Unusual Case, Am. Heart J. **31**:769, 1946.
8. Pastor, B. H., and Woorilow, S. H.: Electrocardiographic Patterns in Stokes-Adams Syndrome, Ann. Int. Med. **34**:80, 1951.
9. Nathanson, M. H.: Effect of Drugs on Cardiac Standstill Induced by Pressure on the Carotid Sinus, Arch. Int. Med. **51**:387, 1933.
10. Nathanson, M. H.: Further Observations on the Effect of Drugs on Induced Cardiac Standstill, Arch. Int. Med. **54**:111, 1934.
11. Schwartz, S. P., and Jezer, A.: The Action of Quinine and Quinidine on Patients With Transient Ventricular Fibrillation, Am. Heart J. **9**:792, 1934.
12. Mark, L. C., Kayden, H. J., Steele, J. M., Cooper, J. R., Berlin, I., Rovenstine, E. A., and Brodie, B. B.: The Physiological Disposition and Cardiac Effects of Procaine Amide, J. Pharmacol. & Exper. Therap. **102**:5, 1951.
13. Kayden, H. J., Steele, J. M., Mark, L. C., and Brodie, B. B.: The Use of Procaine Amide in Cardiac Arrhythmias, Circulation **4**:13, 1951.
14. Kinsman, J. M., Clay, H. L., Coe, W. S., and Best, M. M.: Procaine Amide (Pronestyl) in the Treatment of Disorders of Cardiac Rhythm, Kentucky State M. J. **48**:509, 1950.

15. Miller, H., Nathanson, M. H., and Griffith, G. C.: The Action of Procaine Amide in Cardiac Arrhythmias, J. A. M. A. **146**:1004, 1951.
16. Schaffer, A. I., Blumenfeld, S., Pitman, E. R., and Dix, J. H.: Procaine Amide: Its Effect on Auricular Arrhythmias, AM. HEART J. **42**:115, 1951.
17. Joseph, S. I., Helrich, M., Kayden, H. J., Orkin, L. R., and Rovenstine, E. A.: Procaine Amide for Prophylaxis and Therapy of Cardiac Arrhythmias Occurring During Thoracic Surgery, Surg., Gynec. & Obst. **93**:75, 1951.
18. Morris, L. E., and Haid, B.: Effects of Procaine Amide on Cardiac Irregularities During Cyclopropane Anesthesia, Anesthesiology **12**:328, 1951.
19. Wedd, A. M., Blair, H. A., and Warner, R. S.: The Action of Procaine Amide on the Heart, AM. HEART J. **42**:399, 1951.
20. Di Palma, J. R., and Schultz, J. E.: Antifibrillatory Drugs, Medicine **29**:123, 1950.
21. Dock, W.: Transient Ventricular Fibrillation as a Cause of Syncope and Its Prevention by Quinidine Sulfate, AM. HEART J. **4**:709, 1929.
22. Escamilla, R. F.: Report of a Case of Paroxysmal Ventricular Fibrillation in Relation to Quinidine Therapy, AM. HEART J. **8**:850, 1933.
23. Scherf, D., Silver, O. M., and Weinberg, L.: Clinical Observations With Fagarine, Ann. Int. Med. **30**:100, 1949.
24. Nathanson, M. H., and Miller, H.: The Effect of New Drugs on the Rhythmic Function of the Heart, California Med. **72**:215, 1950.

A MODIFICATION OF THE FLUORESCEIN CIRCULATION TIME

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SEVERAL investigators have reported on the use of fluorescein as a substance with which to perform objectively measured circulation times. They have worked with fluorescein in solution with sodium bicarbonate and have used various structures in observing the end point—the lips and conjunctivae. It is our purpose to present further experience with this method and to point out the advantages of the tongue as the end point and a solution of sodium fluorescein without sodium bicarbonate as the most practical medium. We also include more complete histories and physical examinations of the patients used as controls than have been reported previously.

This paper presents data obtained with fluorescein on fifty people who showed no evidence of cardiovascular disease. It shows also how fluorescein compares with the conventional Decholin circulation time in twenty-five patients in various stages of congestive heart failure.

The circulation time measures the shortest interval between the injection of a substance into a vein and its arrival at some distant site in sufficient concentration to produce a recognizable end point. As is well known, the circulation time is altered in congestive failure; it is related to both the cardiac output and the volume of circulating blood, increasing as the blood volume increases and diminishing as the cardiac output increases. Thus the circulation time is most likely to be prolonged if there is both an increase in the blood volume and a diminution in the cardiac output, findings typical in congestive heart failure.[1]

METHOD

Three cubic centimeters of a solution of 15 per cent sodium fluorescein was injected through a 21 gauge needle into the antecubital vein with the patient in a supine position. The room was semi-darkened after the vein was pierced and an ordinary Wood's ultraviolet light was held at the level of the patient's nose to elicit the fluorescence in the tongue. The beginning point was considered the time the first pressure was applied to the plunger of the syringe. The end point was defined as the first appearance of a definite greenish glow at the tip of the patient's protruded tongue. In the majority of cases the papillae showed the first coloring; in others, there was a diffuse glow. The end point was sharp and two observers consistently agreed within one second of each other as to the time of its appearance.

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The test was first performed on fifty normal individuals who had careful histories and physical examinations to rule out the presence of any known entity which would modify the circulation time. There were thirty men and twenty women. Ages ranged from 13 to 76 years. Pulses ranged from 60 to 100 per minute. No temperature was above 99.4° F. Systolic blood pressures ranged from 105 to 175 mm. Hg with one exception; diastolic pressures from 50 to 90. The minimum hemoglobin was 10 Gm. by the Haden-Hauser method.

The test was also performed on twenty-five patients with heart disease due to various causes. These results were compared with the arm-to-tongue circulation times obtained with 4 c.c. of Decholin injected in the routine manner in the same patients.

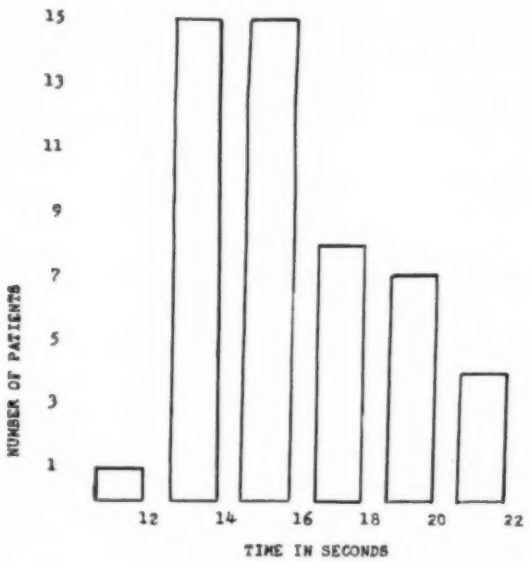

Fig. 1.—Fluorescein circulation times. Mean circulation time, 15.61 seconds; standard deviation, 2.60 seconds; first zone deviation from 13.01 to 18.21 seconds (68 per cent); second zone deviation from 10.41 to 20.81 seconds (96 per cent).

RESULTS

The circulation times obtained in fifty normal individuals ranged from 10.8 to 21.0 seconds. The mean time was 15.61 seconds. The distribution of the times is shown on Fig. 1. According to the formula $S = \sqrt{\frac{1}{N-1}\left[SX^2 - N(X)^2 \right]}$ the standard deviation of these figures was 2.6 seconds. This means that 68 per cent of a normal population will have circulation times between 15.61 plus 2.6 seconds and 15.61 minus 2.6 seconds, (13.0 to 18.2 seconds), and 96 per cent of the normal population will have circulation times between 15.61 plus 2 times 2.6 seconds and 15.61 minus 2 times 2.6 seconds, (10.4 to 20.8 seconds). Therefore, any reading above 20.8 seconds or below 10.4 seconds should be considered as

abnormal. The times obtained with fluorescein on the patients with congestive failure ranged from 21.2 to 78.2 seconds with a mean of 32.8 seconds. The times with Decholin ranged from 21.0 to 70.0 seconds with a mean of 31.7 seconds. The fluorescein and Decholin circulation times on each patient were within 8.4 seconds of each other. On two patients there was no end point obtained with Decholin. There were no failures with fluorescein.

In the series of normal people, there were three who experienced a sensation of nausea lasting a maximum of several minutes, and two who had vomiting of short duration. In the cases of congestive heart failure, there were no instances of vomiting and one patient had transient nausea.

DISCUSSION

Table I shows the results obtained by us, compared with those of Hussey, Cyr, and Katz[2] who in 1942 published their results of arm-to-tongue circulation times with alpha-lobeline, calcium gluconate, and magnesium sulfate in fifty normal individuals and in fifty patients with congestive heart failure. There is a close comparison in the range of times obtained but a marked disparity in the percentage of failures, especially in the patients with congestive failure.

Fishback and associates[3,4] used 4 c.c. of 10 per cent or 3 c.c. of 20 per cent fluorescein and described their end point as the appearance of a brilliant yellow color in the lower palpebral conjunctiva. In fifty normal patients, they found a range of from 7 to 15.6 seconds and in patients with congestive failure a range of from 16 to 25 seconds. These results were considerably faster than most others obtained by different methods, as the conjunctiva permits visualization of vessels larger than capillaries, and manipulation of the conjunctiva, which is necessary to view it, causes local vasodilatation. In our experience, changing the percentage concentration of fluorescein caused a variation in the times observed. These were faster with a higher concentration of the drug and slower with a lower concentration. This would seem to invalidate somewhat the above results as the authors varied the concentration of the fluorescein used in performing the tests.

Lange and Boyd[5-8] used a solution of 5 per cent fluorescein and 5 per cent sodium bicarbonate, and the appearance of a full luminescent greenish hue of the lips was their end point. On 216 adults with normal cardiovascular systems ranging from the ages of 19 to 96 years, they found circulation times varying from 13 to 20.4 seconds with a majority from 15.0 to 17.5 seconds. In our experience the lips are an unreliable site at which to detect an end point. In some patients, a bright green color was observed under the ultraviolet light even before the fluorescein was injected; in others, the lips took on a glow only gradually, making a definitive end point difficult to evaluate.

Winsor, Adolph, Ralston, and Leiby[9] used fluorescein and riboflavin to determine both arm-to-arm and arm-to-foot circulation time. The end point was the presence of a yellow-green luminescence in a histamine wheal which they had raised previous to the injection of the test substance. The chief drawbacks in this method are that it necessitates multiple needle punctures and is time consuming.

TABLE I. COMPARISON STUDIES (ARM-TO-TONGUE CIRCULATION TIMES)

MATERIAL	RANGE OF CIRCULATION TIME (SEC.)	% FAILURES
50 Normal People		
Alpha lobeline*	8.2 – 17.4	10
Calcium gluconate	10.0 – 18.6	4
Magnesium sulfate	10.0 – 20.8	0
Fluorescein	10.4 – 20.8	0
50 Patients With Congestive Failure		
Alpha lobeline*	17.0 – 75.0	24
Calcium gluconate	17.0 – 60.8	18
Magnesium sulfate	16.8 – 71.0	18
Decholin†	21.0 – 70.0	8
Fluorescein†	21.2 – 78.4	0

*Not an arm-to-tongue circulation time.

†On 25 cases.

The method described in this paper, using the tip of the tongue, gave a satisfactory end point in every case, and the results can be duplicated by others not familiar with the technique, indicating that the end point with fluorescein is easy to determine. It can be used with small children, and comatose, anesthetized, mentally ill, malingering, and moribund patients. The dye quickly disappears from the tongue, and we have satisfactorily performed a second determination within five minutes after the first.

SUMMARY

An arm-to-tongue circulation time with 3 c.c. of 15 per cent sodium fluorescein has been described. It is different from those previously reported in that the tongue has been used as an end point. Careful complete histories and physical examinations were obtained on normal patients to establish a valid control series. The circulation times on fifty normal individuals gave results which very closely approximated those previously reported with other drugs. The results on the twenty-five patients with congestive heart failure also closely approximated those previously reported but were outstanding in that there were no failures noted with sodium fluorescein.

We wish to express our appreciation for the valuable assistance given to us by Dr. Leo H. Criep in the preparation of this paper, and to thank the staff of the Veteran's Hospital, Aspinwall, Pa., and the Jewish Home for the Aged, Pittsburgh, Pa., for permission to perform tests on their patients.

REFERENCES

1. Friedberg, C. K.: Diseases of the Heart, Philadelphia, 1949, W. B. Saunders Company, p. 138-142.
2. Hussey, H. H., Cyr, D. P., and Katz, S.: Comparative Value of Calcium Gluconate, Magnesium Sulfate, and Alpha Lobeline Hydrochloride as Agents for Measurement of Arm to Tongue Circulation Time, Ann. Int. Med. **17**:849-858, 1942.
3. Fishback, D. B.: New Objective Circulation Time Test (Fluorescein Method), J. Lab. & Clin. Med. **26**:1966-1968, 1941.
4. Fishback, D. B., Guttman, S. A., and Abramson, E. B.: Objective Method of Determining Velocity (Fluorescein Method), Am. J. M. Sc. **203**:535-539, 1942.
5. Lange, K., and Boyd, L. J.: Technic of Fluorescein Test to Determine Adequacy of Circulation in Peripheral Vascular Disease, Circulation Time, and Capillary Permeability, Bull. New York M. Coll. **6**:78-81, 1943.
6. Lange, K., and Boyd, L. J.: Objective Methods To Determine Speed of Blood Flow and Their Results (Fluorescein and Acetylene), Am. J. M. Sc. **206**:438, 1943.
7. Lange, K., and Boyd, L. J.: Use of Fluorescein Method in Establishment of Diagnosis and Prognosis of Peripheral Vascular Diseases, Arch. Int. Med. **74**:175-184, 1944.
8. Lange K, and Boyd, L. J.: The Use of Fluorescein to Determine the Adequacy of the Circulation, M. Clin. North America **26**:943-952, 1952.
9. Winsor, T., Adolph, W., Ralston, W., and Leiby, G.: Fractional Circulation Times Using Fluorescent Tracer Substances, AM. HEART J. **34**:80-86, 1937.

Clinical Reports

PENETRATION INTO PERICARDIAL CAVITY DURING CARDIAC CATHETERIZATION*

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CATHETERIZATION of the heart has become well established as a valuable diagnostic and experimental tool. The most common type of complication seen in this procedure is disturbance of cardiac rhythm, transient arrhythmias being seen during almost every catheterization[1] and persistent ones being not unusual.[2,3] Myocardial damage has been produced in a high percentage of dogs subjected to cardiac catheterization[4,5]; in the human being this occurrence is rare.[6] Deep cannulation of the cardiac venous system seems to be an important cause of myocardial damage.[4,7-9] McMichael and Mounsey[9] reported a case in which they believed the catheter entered the pericardium after perforating a cardiac vein.[9] The purpose of this report is to present a case in which we believe definite penetration of the catheter into the pericardial cavity occurred.

CASE REPORT

W. M. J., a 42-year-old Negro woman, was admitted to the John Gaston Hospital with myocardial decompensation of unknown etiology, a mediastinal mass, and rubremia. In an effort to elucidate the nature of the cardiac disorder, the heart was catheterized. Under fluroscopic control in the posteroanterior projection the catheter was easily advanced into what appeared to be the pulmonary conus. At this point there was a slight sense of resistance. No more than gentle pressure had been applied to the catheter at any time, and up to this point there had been absolutely no impediment to the advance of the catheter. Ventricular premature contractions had been noted on the electrocardiogram at the time when the catheter was ostensibly passing through the tricuspid valve.

When the obstruction was noted, aspiration was attempted, but no fluid could be withdrawn. The catheter was then withdrawn 4 to 5 cm.; at this time 10 to 15 ml. of clear, very slightly blood-tinged fluid was aspirated. Similar amounts of heparinized saline were subsequently injected slowly through the catheter and recovered almost quantitatively on aspiration. The pressure was quite low. Five milliliters of 70 per cent Diodrast were then injected; this solution was observed under the fluoroscope to spread immediately over the inferior surface of the heart (Fig. 1,*B*). The Diodrast was aspirated and the system was flushed several times with saline.

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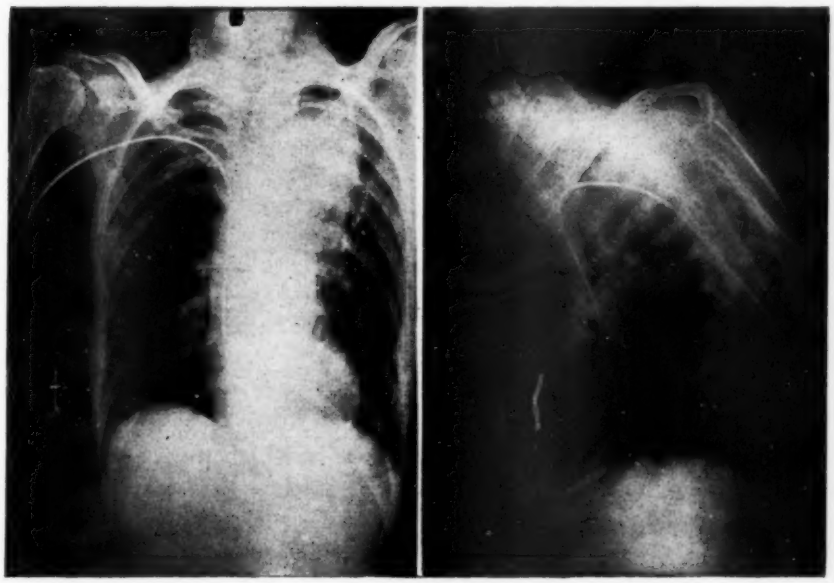
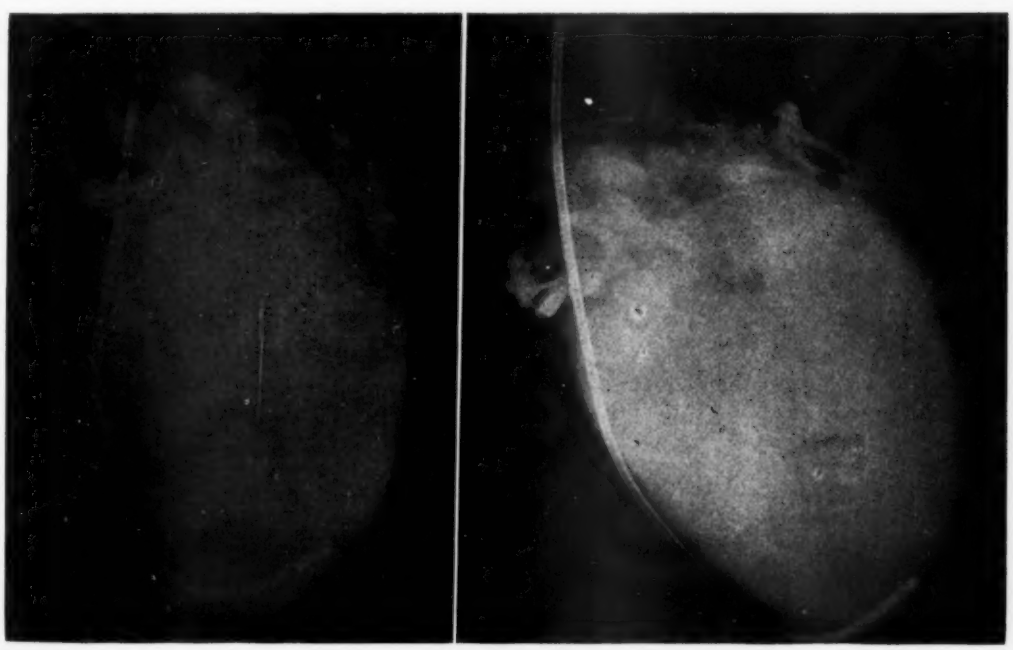


A. *B.*

Fig. 1.—*A*, Posteroanterior chest roentgenogram of patient with the catheter in place. *B*, Lateral chest roentgenogram of patient immediately following injection of Diodrast.



A. *B.*

Fig. 2.—Posteroanterior and lateral roentgenograms of a normal heart with catheter inserted into middle cardiac vein at necropsy.

The catheter was then withdrawn very cautiously without any untoward event. The patient was observed thereafter with frequent pulse and blood pressure determinations, serial electrocardiograms, and fluoroscopy of the chest. The S-T segments in Leads V_1 to V_3 became elevated 2 mm. briefly but returned to their previous level within twenty-four hours. No other sequelae were noted.

Approximately three weeks later an exploratory thoracotomy was performed. A large aortic aneurysm was found and wrapped with Cellophane. The heart, however, was normal as far as could be determined from inspection. Following operation there was progressive cardiac failure from which the patient never recovered. She died two months after the catheterization.

At necropsy the heart was small. There was noted a moderate degree of inactive rheumatic mitral stenosis, with slight dilatation of the left atrium and hypertrophy of the right ventricle. A probe inserted into the middle cardiac vein could be passed no farther than 5 cm. from the coronary sinus; there was a suggestion of fibrosis at this point.

DISCUSSION

McMichael and Mounsey[9] reported a case in which they suggested perforation of a cardiac vein occurred during catheterization. We feel that the present case represents an essentially similar occurrence. The most likely course for the catheter was from the right atrium into the coronary sinus and inferiorly into the middle cardiac vein. At some point (perhaps the area suggestive of fibrosis at necropsy) the catheter most likely perforated the thin wall of the vein, thus finding its way into the pericardial cavity.

Fig. 2 shows roentgenograms of a catheter in the middle cardiac vein of a normal heart removed at autopsy. The close correlation between the position of the catheter in Figs. 1 and 2 can be easily noted.

We cannot prove absolutely that the catheter entered the pericardium. However, the fact that fluid could be injected and aspirated for all practical purposes unchanged both quantitatively and qualitatively, and the distribution of the injected Diodrast (Fig. 1,*B*), lead us to feel that this conclusion is a reasonable one.

This case emphasizes the point, brought out by several investigators, that the path of the catheter should be followed in the sagittal as well as in the frontal plane.

SUMMARY

A case is presented in which a cardiac catheter was passed into the coronary sinus, middle cardiac vein, and, most likely perforating the vein, into the pericardial cavity.

REFERENCES

1. Goldman, I. R., Blount, S. G., Friedlich, A. C., and Bing, R. J.: Electrocardiographic Observation During Cardiac Catheterization, Bull. Johns Hopkins Hosp. **86**:141, 1950.
2. Michael, J., Johnson, A. D., Bridges, W. C., Lehman, J. H., Grey, F., Field, L., and Green, D. M.: Arrhythmias During Cardiac Catheterization, Circulation **2**:240, 1950.
3. Fowler, N. O., Westcott, R. N., and Scott, R. C.: Disturbances in Cardiac Mechanism of Several Hours' Duration Complicating Cardiac Venous Catheterization, Am. Heart J. **42**:652, 1951.
4. Goodale, W. T., Lubin, M., Eckenhoff, J. E., Hafkenschiel, J. H., Durlacher, S. H., Landing, B. H., and Banfield, W. G.: Coronary Sinus Catheterization Technique for Studying Myocardial Blood Flow and Myocardial Metabolism in Vivo, Proc. Soc. Exper. Biol. & Med. **66**:571, 1947.

5. Ellis, E. J., Essex, H. E., and Edwards, J. E.: Lesions of the Heart in Dogs Following Cardiac Catheterization, Proc. Staff Meet., Mayo Clin. **25**:73, 1950.
6. Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Seibel, R. S., and Evans, J. M.: Studies on Congenital Heart Disease: I. Technique of Venous Catheterization as a Diagnostic Procedure, J. Clin. Investigation **26**:547, 1947.
7. Goodale, W. T., Lubin, M., Eckenhoff, J. E., Hafkenschiel, J. H., and Banfield, W. G., Jr.: Coronary Sinus Catheterization for Studying Coronary Blood Flow and Myocardial Metabolism, Am. J. Physiol. **152**:340, 1948.
8. Smith, W. W., Albert, R. E., and Rader, B.: Myocardial Damage Following Inadvertent Deep Venous Cannulation of the Coronary Sinus During Right Heart Catheterization, Am. Heart J. **42**:661, 1952.
9. McMichael, J., and Mounsey, J. P. D.: A Complication Following Coronary Sinus and Cardiac Vein Catheterization in Man, Brit. Heart J. **13**:397, 1951.

DYSPHAGIA LUSORIA: AN UNUSUAL CASE

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THE CLINICAL problem of cyanosis and dysphagia occurring with varying degrees of intensity during the first year of life is uncommon. These signs indicate the presence of a congenital defect involving the trachea and esophagus. Since many of these anomalies are capable of surgical correction,[1] careful evaluation of such cases is necessary. Utilization of special roentgenologic techniques has aided in the visualization of the defect.[2]

Dysphagia lusoria is a descriptive term used to describe the syndrome produced by an aberrant right subclavian artery compressing the esophagus.[3] However, any extrinsic cause of tracheo-esophageal obstruction may elicit a similar picture.[4] The following case fulfills the clinical and anatomic requirements associated with dysphagia lusoria in addition to several unique features. Careful analysis of the gross pathology found in such cases may help to elucidate the basic alteration involved in establishing the defect.

CASE REPORT

The patient, a 5-month-old white girl, was admitted to Walter Reed Army Hospital July 6, 1951, with a tentative diagnosis of double aortic arch. The family and developmental histories were negative and there were no siblings. After the mother's uneventful pregnancy and labor, the infant was born at term. At birth, she was moderately cyanotic and did not cry spontaneously. The cyanosis disappeared completely with aspiration, and the infant, apparently well, was discharged from the hospital on the fifth day of life. On several occasions during the neonatal period the infant became cyanotic when crying, but this cleared immediately when calmed by the mother. Feeding difficulties manifested by choking, regurgitation, and slight cyanosis occurred soon after birth. The mother found that if the child was fed in the supine position, these difficulties did not occur; and in this position the infant was able to take fluids and solids well. With increased activity or crying, some "crowing" and rapid respirations were noticed. During the seventh week of life, three attacks of deep cyanosis occurred unassociated with feeding, and cleared spontaneously. She was hospitalized during one of these attacks, placed in oxygen, and discharged two days later with a diagnosis of congenital heart disease, type undetermined.

Physical Examination.—The patient was a well-developed and well-nourished 5-month-old infant weighing 13 pounds and 10 ounces. The respirations upon admission were 80 per minute with minimal retraction substernally and in the suprasternal notch. Later observations revealed a normal respiratory rate with no retraction. Over the left upper anterior chest wall in the second and third intercostal spaces was a palpable systolic thrill and a Grade IV prolonged harsh systolic murmur. The murmur began with the first and continued through the second heart sound, but at no time was it continuous nor was a diastolic component heard. Cardiac size and configuration were normal by x-ray examination, and good femoral pulsations were palpable bilaterally.

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The red blood cell count was 4,150,000 per ml., hemoglobin 12.4 Gm., with a normal white blood blood cell count and differential. The electrocardiogram showed no abnormalities. The initial impression was a vascular anomaly constricting the esophagus.

During the hospital course, the infant exhibited no feeding difficulties when fed in the supine position, but had some choking when fed in the upright position. Only two attacks of cyanosis were observed. The first, mild and transitory, occurred with activity. The second, more severe, occurred while the infant was crying during a femoral puncture and lasted several minutes. The only other difficulty was occasional transitory wheezing associated with rapid respirations following exertion. Under fluoroscopy a No. 10 French catheter was inserted into the

Fig. 1.—Roentgenogram of chest in left oblique position. Esophagus is filled with barium and shows a filling defect with narrowing and compression of the lumen at T_4.

esophagus and barium was injected above the level where the constriction was thought to be present. On the right lateral view, the barium passed rapidly down to the level of T_4 where it abruptly flowed anteriorly over an obstruction and passed quickly into the stomach. Chest roentgenograms taken during fluoroscopy confirmed a definite filling defect on the posterior wall of the upper one-third of the esophagus (Fig. 1). This defect appeared oblique in its direction with the lower portion of the obliquity being to the left. It was thought that this filling defect was characteristic of that caused by an aberrant right subclavian artery as first demonstrated by Neuhauser.[2]

A thoracotomy was performed on July 27, 1951, under endotracheal ether anesthesia. The aorta descended on the right, and what appeared to be a small retro-esophageal accessory aortic

arch was noted, ligated, and divided. Immediately postoperative, respirations were rapid and shallow at 64 per minute with a pulse rate of 136 per minute. Auscultation of the heart revealed the same harsh, Grade IV systolic murmur heard preoperatively. Four hours after operation, the infant appeared to be doing fairly well when she suddenly became restless, cyanotic, and dyspneic. The pulse was unobtainable and despite immediate transfusion, continuous oxygen, and stimulants, the infant had increasingly labored respirations and died.

At *autopsy*, the most striking features were confined to the heart and great vessels. The ductus arteriosus arising from the left pulmonary artery was severed, tied, and was not patent. The aorta curved to the right so that the first portion of the descending aorta was present to the right of the vertebral column. The aorta then passed over behind the root of the lung on the left side and then behind the heart, separated in part by the esophagus which inclined toward

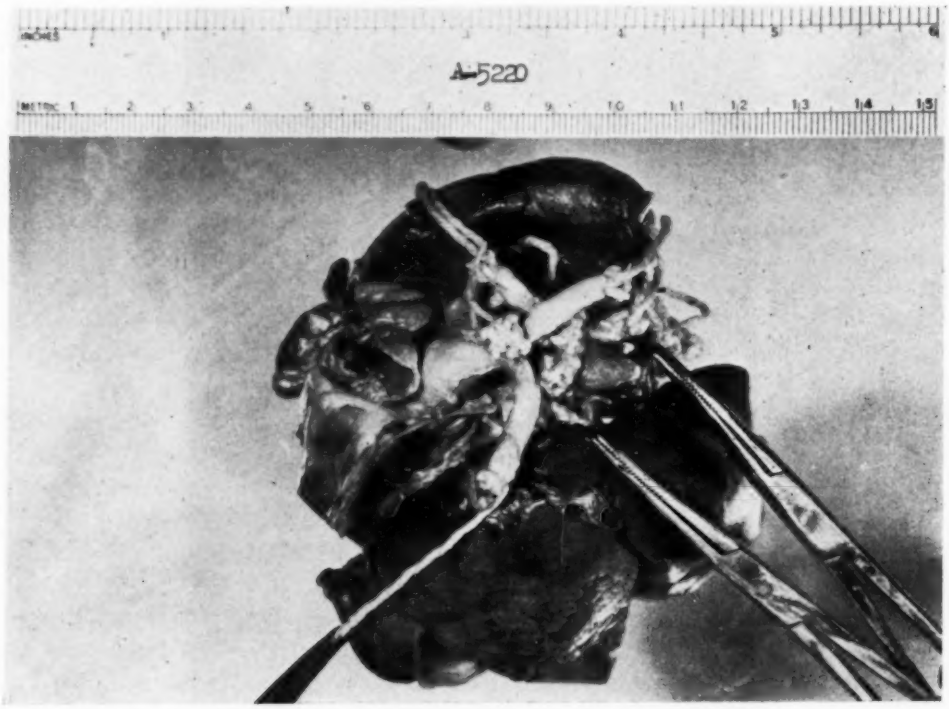

Fig. 2.—Top clamp holds black suture on anastomotic branch of right subclavian. Middle clamp holds suture on ductus, and bottom clamp pulls left subclavian aside to expose left common carotid and right common carotid. Right subclavian is directly posterior to left common carotid.

the left. Arising from the arch of the aorta were four large vessels, namely, left subclavian, left common carotid, right common carotid, and right subclavian arteries. The right subclavian artery arose as an independent vessel to the right and posterior to the right common carotid. A small branch from the right subclavian artery passed to the left behind the esophagus to anastomose with the ductus arteriosus (Figs. 2 and 3). This branch of the right subclavian had been tied and cut near its origin.

A high interventricular septal defect was present and was partially obscured by the medial cusp of the tricuspid valve. The aorta appeared to override the septal defect. Due to an increased thickness of the infundibular region just proximal to the pulmonary valve, the pulmonary conus was reduced in size with a resulting relative pulmonary conus stenosis. Immediately above the infundibulum, the pulmonary trunk was dilated. The left ventricular wall was 50 mm. thick and the right ventricular wall was 30 mm. thick. In all other respects the heart was normal.

The lungs were markedly congested and edematous. Similar congestion was found in the liver, spleen, and kidneys. The esophagus was entirely normal. Microscopic examination of the lungs revealed the presence of atelectasis and congestion, the other tissues being relatively normal.

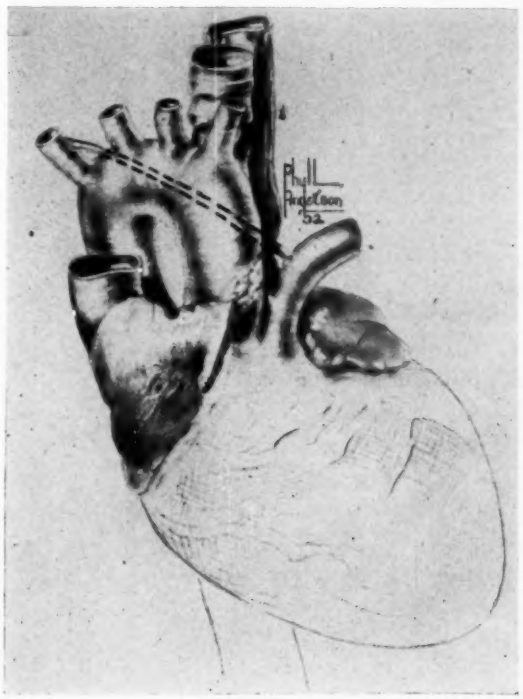

Fig. 3.—Semischematic drawing of heart demonstrating the angulated retroesophageal vessel.

DISCUSSION

The primary embryonic arteries are the left and right aortas connected by pairs of aortic arches. During development of the embryo, these arches are altered until the 13 mm. stage is reached when the usual adult system begins to be recognized. The first and second arches rapidly disappear while the carotids originate from the third arches. If the fifth aortic arches do develop, they ultimately disappear along with the sixth arch on the right. The subclavian artery arises from the right fourth arch while the left becomes the adult aorta. On the left, the sixth arch remains as the ductus arteriosus. During the period of arterial development, various types of anomalies may result. A right subclavian artery represents the persistent caudal portion of the fourth aortic arch joining the dorsal aorta. In some instances, these "aberrant" arteries anastomose with other anomalous vessels.[5]

In the case presented, the ductus arteriosus had been obliterated and the branch of the right subclavian artery involved in the anastomosis had a markedly reduced lumen. This angulated anastomotic vessel compressed the esophagus and the trachea resulting in the clinical signs and symptoms as noted. The high interventricular septal defect accounted for the murmur heard on admission.

Although the operation corrected the tracheo-esophageal constriction, unfortunately the patient died due to impaired cardiac function as a result of the other anomalies. The anomaly present in this case is similar to the one reported by Faber and Griffin.[6] These authors observed a case of tracheo-esophageal obstruction due to a retro-esophageal patent ductus arteriosus.

The presence of a high interventricular defect, relative pulmonary stenosis, dextroposition of the aorta and right ventricular hypertrophy is compatible with the diagnosis of the tetralogy of Fallot. These defects plus the retro-esophageal constriction are noted for the first time in American literature.

The diagnosis of an anomalous aortic arch with constriction of the esophagus and trachea should be considered in an infant who presents the following picture: recurrent respiratory infections, stridor, noisy respirations, difficulty in swallowing, and fleeting attacks of cyanosis occurring soon after birth.[7] Surgical correction is now possible since Gross[8] first attempted division of a vascular ring in 1945. However, the additional anomalies associated with a tetralogy limited the usefulness of such a procedure in this case. No doubt the intracardiac defects accounted for the early death of the patient following operation. If the symptoms of dysphagia lusoria appear early in life and are clinically severe, before an operation is attempted other cardiac anomalies must be ruled out. Where tracheo-esophageal constriction is due to constriction alone and no other anomalies are present, an operation is indicated to avoid the danger of pulmonary infections and repeated cyanotic episodes.

SUMMARY

An unusual congenital anomaly causing tracheo-esophageal obstruction associated with tetralogy of Fallot is presented. The clinical picture of cyanosis and dysphagia with the roentgen demonstration of extrinsic esophageal pressure represents the syndrome referred to as dysphagia lusoria. A retro-esophageal vascular anomaly was largely responsible for the clinical findings. Such abnormalities are not readily explained and demonstrate the varied picture of faulty embryogenesis. Dysphagia lusoria associated with a tetralogy of Fallot has not been reported previously.

REFERENCES

1. Gross, R. E., and Ware P. F.: The Surgical Significance of Aortic Arch Anomalies, Surg., Gynec. & Obst. **83**:435, 1946.
2. Neuhauser, E. B. D.: The Roentgen Diagnosis of Double Aortic Arch and Other Anomalies of the Great Vessels, Am. J. Roentgenol. **56**:1, 1946.
3. (a) Goldbloom. A. A.: Anomalous Right Subclavian Artery, Surg., Gynec. & Obst. **34**:378, 1922.
   (b) Bean, H. P., and Neuhauser, E. B. D.: Syndrome of Aberrant Right Subclavian Artery With Patent Ductus Arteriousus, Am. J. Roentgenol. **58**:708, 1947.
   (c) Copleman, B.: Anomalous Right Subclavian Artery, Am. J. Radiol. **54**:270, 1945.

4. (a) Wolman, I. J.: Syndrome of Constricting Double Aortic Arch in Infancy, J. Pediat. **14**:527, 1939.
(b) Gordon, S.: Double Aortic Arch, J. Pediat. **30**:429, 1947.
5. Fluss, Z., and Poppen, K. J.: Embryogenesis of Tracheoesophageal Fistula and Esophageal Atresia, Arch. Path. **52**:168, 1951.
6. Faber, H. K., and Griffin, M. M.: Tracheoesophageal Obstruction From Rotroesophageal Patent Left Ductus Arteriosus With Right Aorta and Other Vascular Anomalies, Stanford Med. Bull. **8**:177, 1950.
7. Potts, W. J., Gibson, S., and Rothiwell, R.: Double Aortic Arch, Arch. Surg. **57**:227, 1948.
8. (a) Gross, R. E.: Surgical Relief for Tracheal Obstruction From a Vascular Ring, New England J. Med. **233**:586, 1945.
(b) Gross, R. E.: Surgical Treatment for Dysphagia Lusoria, Ann. Surg. **124**:532, 1946.

Review of Recent Advances

THE PRESENT STATUS OF ELECTROKYMOGRAPHY

A Review

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CLINICIANS and physiologists have long desired an accurate record of the motions of the human heart. While the development of fluoroscopy made direct visual observation of the cardiovascular silhouette possible, careful phasic analysis of the cardiac movements was extremely difficult. The roentgenkymograph, developed by Stumpf,[1] made possible the recording of the border movements of the heart, several cycles being recorded on a roentgenographic film. However, certain inherent limitations of the instrument, including the lack of sharp definition of the records, plus the inability to record more than a few cycles of cardiac activity on a single x-ray film, were definite drawbacks to the use of this method.

Progress in electronic engineering permitted further advances in the attempt to record cardiac motion. The development of the photomultiplier tube, in particular, made possible the development of the electrokymograph. In 1944 workers from Temple University School of Medicine and the United States Public Health Service, Henny, Boone, Gillick, Oppenheimer, and Chamberlain, collaborated in the development of the electrokymograph.[2,3,5-7] This is essentially a photoelectric device which records the movements of the heart as they appear on a fluoroscopic screen. The photomultiplier tube translates movements of the heart border, as well as changes in density of the cardiac silhouette, into an electric current of varying intensity. The current changes caused by cardiac motion actuate a galvanometer which records a beam-type tracing on ordinary photosensitive electrocardiographic paper. Cardiac sounds or the carotid pulse are also recorded simultaneously, providing further information about cardiac activity, as well as reference points for timing the events of the cardiac cycle.

In actual use electrokymographic tracings of the various chambers and great vessels have been found to be clearly delineated and of good amplitude. Those obtained from the great vessels resemble closely intra-aortic pressure records, while those obtained from the ventricle bear a considerable resemblance to the ventricular volume curves obtained in animals by placing the heart in a plethysmographic chamber. These records provide a new, relatively easy, and hitherto

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undeveloped means of studying the border movements and the changes in thickness (density) of the human heart. One of the advantages of the use of this instrument is the relative ease of recording, since curves are obtainable in a few minutes, and can be repeated rapidly under different physiologic conditions, without long or complicated preparation. A considerable body of physiologic data regarding cardiac dynamics in health and disease has been accumulated during the past seven years by means of the electrokymograph. It is the purpose of the present review to summarize the knowledge gained concerning cardiac activity by the use of this new physiologic tool and to point out its possible clinical uses and limitations.

PRINCIPLE AND DESCRIPTION OF ELECTROKYMOGRAPH

The electrokymograph is an instrument designed to detect and record variations in the intensity of a beam of x-rays.[2-7,18,83] When the beam of x-rays is directed past the borders of the heart or great vessels, the motions of these structures may be recorded. When the beam is directed through these structures, the cyclic changes in their density may be recorded.

The electrokymograph consists fundamentally of a small roentgen radiation detector, its amplifier and power supply, and a recording device, such as an electrocardiograph. The radiation detector consists of a multiplier phototube with a small fluorescent screen placed directly over the phototube's sensitive surface. This detector unit is attached to the patient side of the fluoroscopic screen of a conventional roentgenoscope (Fig. 1).

In recording cardiovascular motions (Fig. 1), the radiation detector is centered roentgenoscopically over the border of the cardiovascular silhouette and the electrocardiographic recorder is set in motion. The pulsating heart border may be seen to cover an increasing amount of the detector's fluorescent screen during the expansile phase of the cardiac cycle and a decreasing amount of the screen during the contractile phase. The intensity of the roentgen rays passing through the detector's fluorescent screen thus varies in accordance with the motion of the heart border. These varying rays cause the emission of varying fluorescent light from the screen in proportion to their intensity. The phototube reacts to this light by generating an electric current proportional to the intensity of the fluorescent light. The recorder to which the phototube is connected produces a curve whose amplitude is a function of the motion of the heart border under study.

In recording density changes, the detector is centered over the cardiovascular organ so as to exclude border motions. The intensity of the x-ray beam passing through the organ and falling on the radiation detector will vary in proportion with the anteroposterior thickening and thinning of the organ. The phototube, connected to the recorder, produces a curve whose amplitude is a function of the varying density of the cardiovascular organ under study.

The evaluation and interpretation of an electrokymogram is greatly facilitated by the simultaneous recording of some other well-known cardiodynamic event.[3,15,19,72] The carotid sphygmogram has been found to be very satisfactory

for most purposes though the stethogram and electrocardiogram can likewise be used.

NORMAL AURICULAR CURVE

Auricular electrokymograms can be recorded over the borders of both the right and left auricle. Right auricular curves are recorded principally in the posteroanterior position over the lower right arch. Left auricular curves are recorded over (1) the left auricular appendage in a 10 degree left oblique rotation, (2) over the left posterior border in a left anterior oblique position, and (3) over the right posterior auricular border in a right anterior oblique position.

Fig. 1.—Photograph showing the electrokymograph x-ray detection unit (*C*) and its rotating mechanism (*D*) in position on the fluoroscopic screen (*E*). The carotid pulse cup (*A*) permits pneumatic simultaneous pulse recording from the subject (*B*). *F*, Fluoroscopist.

The movement of the auricular wall is considerably less than that of the ventricles and results from a variety of mechanical factors. The auricular wall moves as a result of intrinsic auricular activity, because of transmitted motion from adjacent structures and as a part of the movement of the heart as a whole. The proportions of each factor may vary and account for the variations seen on the auricular curve.

The auricular electrokymographic curve usually consists of three waves: one in auricular systole and two during auricular diastole (Figs. 2 and 3). Wave 1 (see Figs. 2 and 3, actual and schematic auricular curves) is associated with

auricular systole. The crest indicates the onset of auricular contraction, and point *1a* the closure of the atrioventricular valve. Period *1a* to *2* is associated with ventricular isometric systole. Wave 2 is associated with ventricular ejection and believed due to the descent of the atrioventricular septum toward the apex. This pulls the auricular wall sharply towards the midline. At point *2a* auricular filling predominates and the curve rises to wave 3. Frequently semilunar valve closure is reflected and is evidenced on the curve (Fig. 3) at *2b*. (Occasionally point *2b* may be prominent and be confused with the crest of wave 3.) Wave 3 indicates atrioventricular valve opening. The period *3* to *3a* is related to auricular emptying and the rapid-filling phase of the ventricle. At point *3a* the curve rises as ventricular filling becomes predominant and the auricle moves outward on the expanding ventricle. This movement terminates at wave 1, the onset of the next auricular systole.

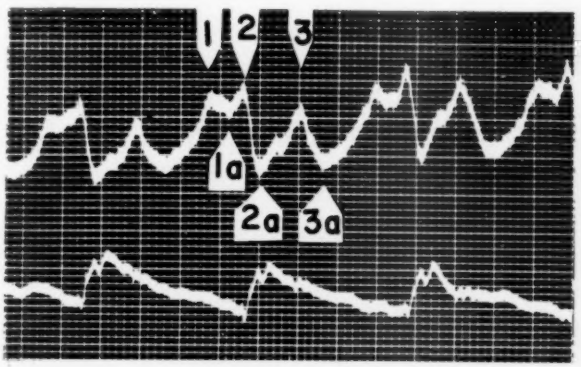

Fig. 2.

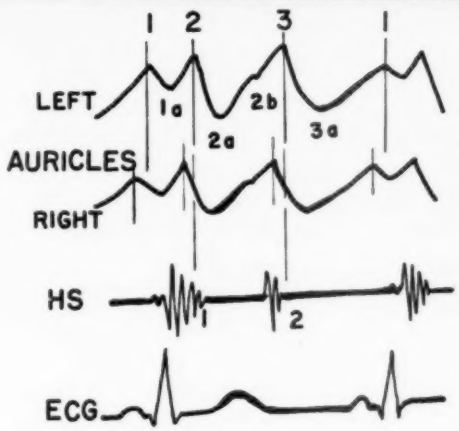

Fig. 3.

Fig. 2.—The upper curve is a normal auricular border electrokymogram. Wave 1 marks the onset of auricular systole. Wave 2 marks the onset of the ventricular contraction effect, and Wave 3 marks the atrioventricular valve opening and subsequent auricular loss of volume. (For additional description see text.) The lower curve is a carotid artery tracing.

Fig. 3.—Schematic representation of normal left and right auricular border electrokymograms and their relationship to heart sounds (*HS*) and the electrocardiogram (*ECG*). Waves 1, 2, and 3 characterize the normal auricular electrokymograph. (See text for further details.)

Right and left auricular curves are similar in shape though vary somewhat in timing. Luisada, using two phototubes, recorded both curves simultaneously

and found the right auricular contraction to precede the left auricular contraction by 0.025 to 0.030 second.[12,81] Engstrom and associates,[44] and Mednick and associates,[60] obtained similar results, reporting the right auricle to precede the left by 0.01 to 0.035 second. In general, the left auricular presystolic wave (wave 1 to 1a) is larger than the right. Occasionally, wave 1 may be fused (masked) and absent, providing the two-wave curve some investigators have described. The complex of wave 2-2a-3 is the most constant feature of the auricular curves.

NORMAL TRACINGS OF AORTA AND PULMONARY ARTERY

Electrokymographic tracings of the great vessels resemble closely those obtained by direct cannulation of the great vessels in animals. Long[81] has shown that electrokymographic tracings of the pulmonary artery in human subjects, taken simultaneously with intrapulmonic catheter tracings, revealed a good temporal correlation between the expansile outward movement, recorded by the electrokymograph, and the rise of pressure in the pulmonic artery during ejection. The time of onset of the incisura of the pulmonary artery electrokymographic tracing and the incisura (signifying pulmonic valve closure) obtained by intrapulmonic catheterization also agreed closely. Salans, Shack, and Katz[77] found a fairly close correlation between the onset of the elevation in intra-aortic pressure in systole, recorded by retrograde catheterization of the aorta, and the initial outward movement of the electrokymographic tracing of the aortic border. From our experience and from these studies it may be said that electrokymographic tracings of the great vessels provide a type of central pulse record which agrees closely, both in contour and timing, with tracings obtained by direct cannulation of the aorta and pulmonary artery.

A typical electrokymographic tracing obtained from a record of border motion of the aorta is shown in Fig. 4. It will be seen that the sharp upward movement from the base line (point *2*) indicates the beginning of ejection of blood into the aorta. After reaching a summit, the ejection curve then declines. The incisura or predicrotic notch is usually well delineated when records are taken with a string galvanometer* plus a suitable filter and amplifying circuit. The end of systole (point *4*, Fig. 4) is marked by a sharp downward declination, during which time the semilunar valves close (phase of protodiastole). The isometric contraction phase preceding ejection, during which pressure is rising rapidly in the ventricle, does not produce constant and dependable landmarks on the great vessel electrokymographic tracings. However, its duration can be measured by determining the time interval between the first major vibration of the first heart sound, and the upward movement on the aortic electrokymographic tracing,

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*It has been shown by Zinsser, Kay, and Benjamin,[66,81] and also by Landowne,[81] that the recording characteristics of the instrument employed may limit the fidelity of records produced. The predicrotic notch may be attenuated or poorly inscribed if the frequency response of the recording device is unable to record such relatively rapid border movements. This fact may account for the occasional failure of some investigators to record the incisura or predicrotic notch of the great vessels sharply and clearly in some reported studies.

which marks the beginning of ejection. Positional movements of the great vessels, due to movements of the aorta as a whole, and not due to an expansile pulse wave per se, may introduce certain errors into the measurement of this phase.

The pulmonary artery electrokymographic tracing (Fig. 5) resembles that of the aorta in its general character. However, the predicrotic notch is often larger and located farther down on the descending limb of the tracing. Furthermore, the summit is usually more rounded and is frequently reached slightly later in systole than is the summit of the aortic tracing. These differences between aortic and pulmonary tracings are variable, however, and quite occasionally it is difficult to distinguish one from the other.

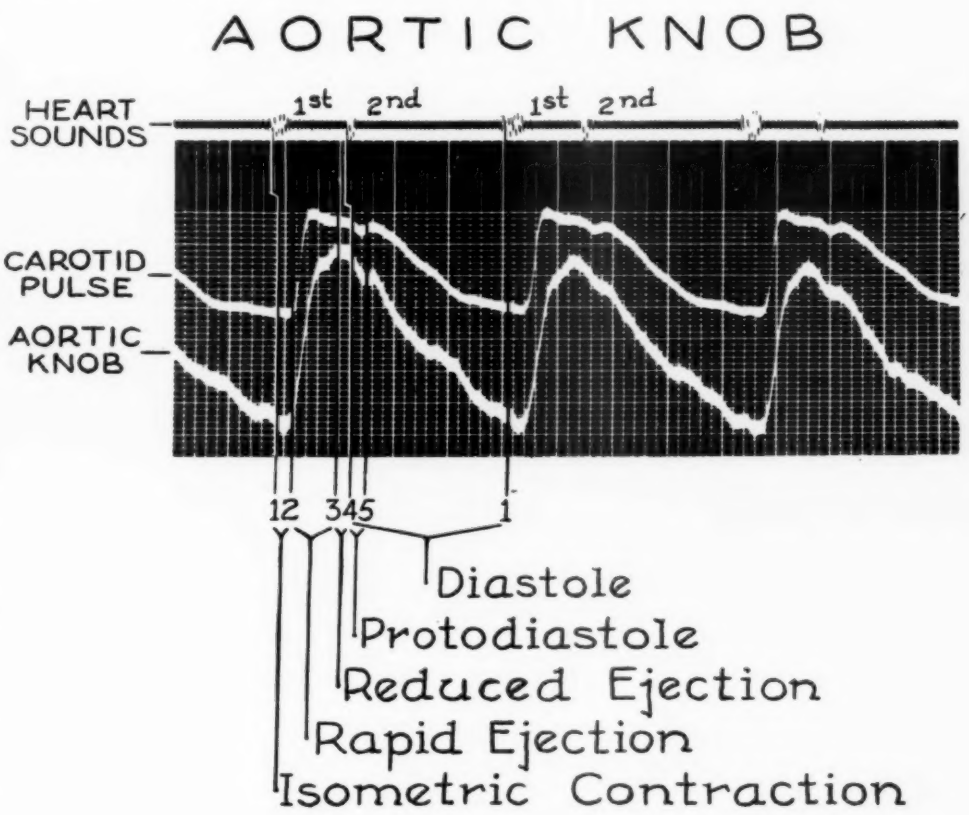

Fig. 4.—An electrokymographic tracing from the border of the aortic knob is shown, with markings delineating the phases of the cardiac cycle. Carotid sphygmogram and heart sounds appear above the electrokymographic tracing. The break present in the black lines *1* and *4*, drawn from heart sounds to electrokymographic tracing, allows for the recording lag between heart sound and electrokymograph. The distance between vertical white lines represents 0.04 second time markings at a camera speed of 50 mm. per second.

Line *1*, from the first heart sound, denotes the onset of isometric contraction. Line *3*, through the summit of the aortic curve, divides rapid and reduced ejection. Line *4* is drawn from the onset of the second heart sound. Line *5* is drawn through the incisura of the aortic tracing.

NORMAL VENTRICULAR CURVE

Fig. 6 illustrates a tracing of the normal left ventricular border. This bears a close resemblance to the ventricular volume curve, obtained by inserting an

animal heart into a plethysmograph. The major downward movement begins very soon after the first heart sound, and represents the inward movement of the ventricular border which occurs during contraction of the ventricle. The upsweep of the ventricular curve, following the second heart sound, is due to the outward movement of the ventricular border during diastole. The exact shape of this curve varies in different subjects, is also changed somewhat by alterations in cardiac rate, and varies slightly in shape over different portions of the ventricle.

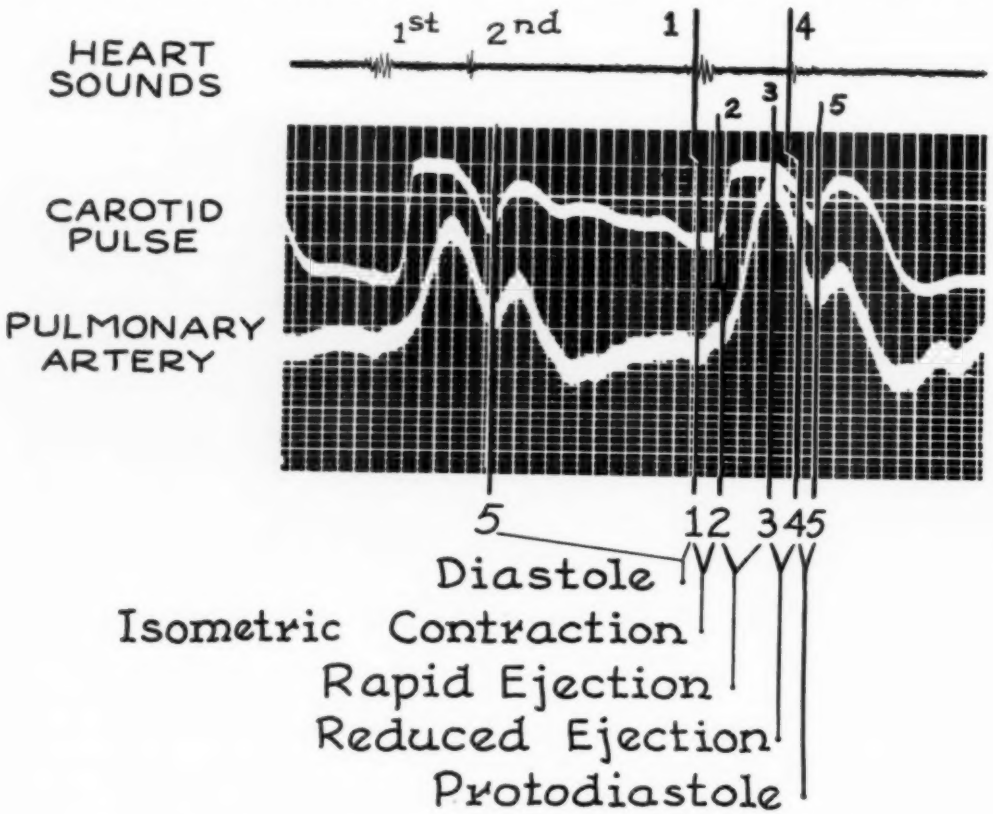

Fig. 5.—Electrokymographic tracing of border of pulmonary artery. Method of demarcation of various phases of systole similar to Fig. 4.

The first major vibration of the first heart sound (point *1*, Fig. 6) is often used to denote the onset of contraction on the ventricular border tracing. During this first portion of systole the ventricle is not expelling blood, and hence little downward (inward) movement of the ventricular border occurs. Following the opening of the aortic and pulmonic valves, the ventricular border continues to move inward, with a smooth downward sweep. The end of systole may or may not coincide with the lowest downward movement of the curve, but the point of termination of contraction may be demarcated by the second heart sound (point *4*, Fig. 6). At both the beginning and end of systole upward movements may occur, which are due to positional movements of the heart within the thorax, and which are not due to contraction or relaxation of the ventricle itself. The period between *1* and *4*, Fig. 6, denotes the period of contraction.

With the onset of diastole the aortic and pulmonic valves close, and the ventricle remains a closed chamber for a short period of time, designated as the isometric relaxation phase, (area between lines *4* and *6*, Fig. 6). During this interval, Willis and associates[72] have pointed out that positional movements often produce an upward movement followed by a short downsweep. When the auriculoventricular valves open, and the auricular blood discharges into the

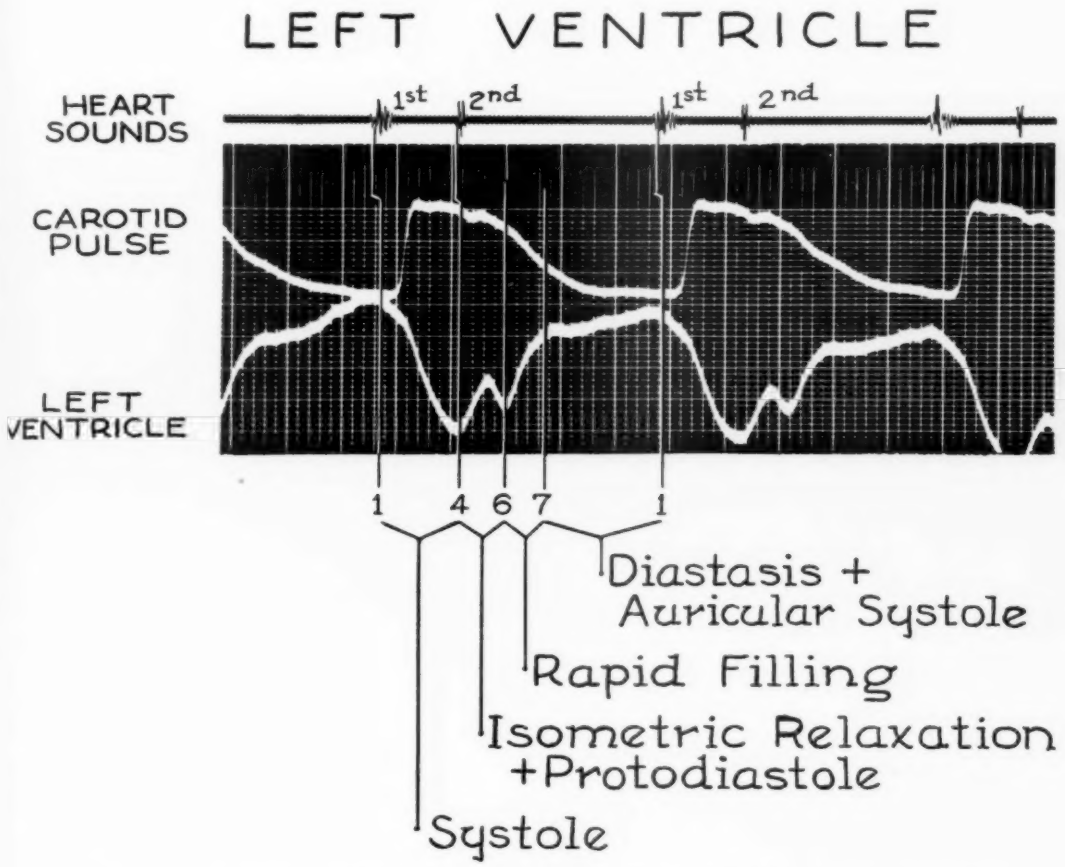

Fig. 6.—An electrokymographic tracing taken from the border of the left ventricle, showing the method of delineating the phases of the cardiac cycle. Line *1* is drawn from the onset of the first heart sound and denotes the beginning of systole, shown as a downward movement of the ventricular curve. Line *4* is drawn from the onset of the second heart sound and indicates the end of systole. Line *6* denotes the beginning of the upward movement of the rapid-filling phase.

ventricle, the cardiac border begins a smooth, fairly sharp, outward movement (upward on the tracing) which is due to rapid filling of the ventricle (designated between the areas *6* and *7*, Fig. 6). This upward (outward) movement of the rapid-filling phase, during which the ventricle is increasing in volume, is followed by a relatively level plateau (diastasis) during which little blood enters the ventricle. During the last portion of diastole a further slight upward movement, due to a further influx of blood caused by auricular contraction, is evident in many, but not all, ventricular tracings.

PHYSIOLOGIC VARIATIONS IN PHASES OF CARDIAC CYCLE

The development of the electrokymograph has made it possible to determine directly variations in the duration of various phases of the cardiac cycle in human beings. Such data can be obtained by other means only by indirect methods (such as arterial or venous pulse tracings) or by means of cardiac catheterization. Alterations in the length of the various phases of contraction and relaxation can be studied rapidly and recorded with ease. Serial records can be made and repeated with the subject in various positions, as well as before and after the administration of digitalis or other drugs.

Variations in the Systolic Phase in Normal Subjects.—The mean duration and range of the various phases of the cardiac cycle in normal subjects are summarized in Table I. Willis and associates[72] found in these studies that the mean duration of ejection of blood during systole into the aorta (determined from tracings of the aortic knob) averaged 0.23 second. Close agreement between the duration of ejection in the aorta and the pulmonary artery was also noted. The isometric

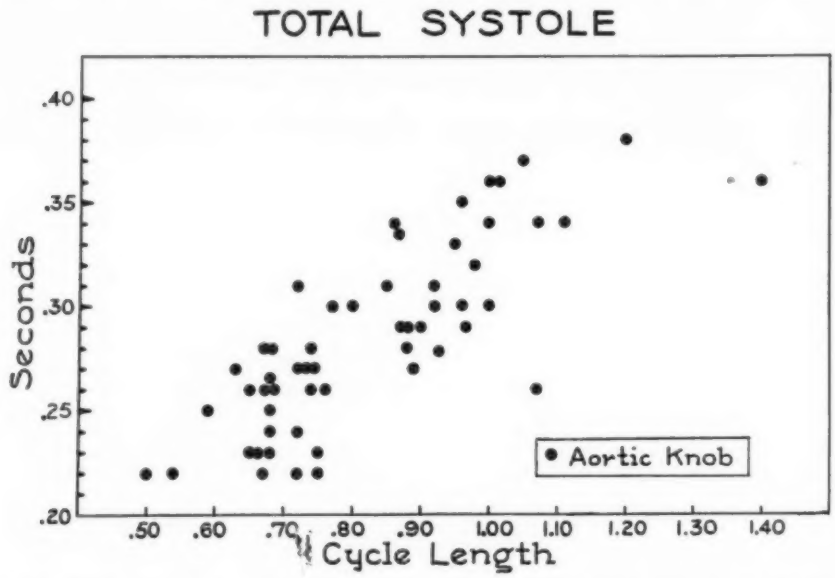

Fig. 7.—The duration of systole (in seconds) reveals a definite direct correlation with cycle length (also in seconds). It will be seen that the duration of contraction increases with the longer cycle lengths.

contraction phase (during which pressure mounts in the ventricle, but no blood is ejected into the great vessels) averaged 0.05 second. In this study the phase of protodiastole, during which period the semilunar valves close, averaged 0.04 second. Although some asynchonism of contraction of the ventricles frequently occurred, these authors found that the right and left ventricles agreed closely in the duration of these phases.[72]

The duration of systole (Fig. 7) has been found to vary directly with the cardiac cycle length, increasing in duration with slower heart rates. The isometric contraction phase, determined electrokymographically, does not appear to change

in duration within the usual physiologic variations in heart rate. In other studies Eddleman, Willis, and Heyer[73] found the duration of total systole and of the ejection phase were almost always markedly and significantly shortened when the subjects stood upright. This shortening, while it was in part related to the more rapid heart rate seen in the upright posture, was also apparently related to diminished stroke volume associated with diminished venous return, as well as to reflex neurogenic factors which also shortened the duration of contraction.

TABLE I. DURATION OF THE PHASES OF THE CARDIAC CYCLE IN NORMAL SUBJECTS

		SYSTOLIC PHASES			
		ISOMETRIC CONTRACTION (SEC.)	TOTAL EJECTION (SEC.)	TOTAL CYCLE LENGTH (SEC.)	PROTODIASTOLE (SEC.)
Aortic knob	Mean duration	0.05	0.23	0.83	0.04
	Range	0.03–0.08	0.17–0.32	0.50–1.40	0.03–0.05
60 subjects	Standard deviation	0.0185	—	—	—
Pulmonary artery	Mean duration	0.04	0.25	0.81	0.04
	Range	0.03–0.06	0.18–0.36	0.60–1.33	0.03–0.05
40 subjects	Standard deviation	—	—	—	—

		DIASTOLIC PHASES				
		PROTODIASTOLE PLUS ISOMETRIC RELAXATION (SEC.)	RAPID FILLING (SEC.)	DIASTASIS (SEC.)	TOTAL DIASTOLE (SEC.)	TOTAL CYCLE LENGTH (SEC.)
Left ventricle	Mean duration	0.14	0.17	0.23	0.54	0.82
	Range	0.05–0.23	0.08–0.30	0.04–0.74	0.33–1.19	0.55–1.54
60 subjects	Standard deviation	0.014	0.035	—	—	0.173
Right ventricle	Mean duration	0.13	0.15	0.21	0.49	0.81
	Range	0.08–0.20	0.07–0.28	0.02–0.48	0.32–0.77	0.53–1.17
25 subjects	Standard deviation	0.017	0.044	—	—	—

The duration of the rapid-filling phase in early diastole has also been found to vary with different positions of the body.[73] This phase, measured as a phase of rapid outward expansion on the ventricular electrokymographic curve, was lengthened when subjects arose from the supine posture. This increase was most probably due to pooling of blood in the legs, resulting in a slower rate of diastolic filling. A similar slowing of the rate of ventricular filling in early diastole was found to occur when tourniquets were applied to the lower extremities.[73] Slowing of the rate of filling was also noted after bleeding normal subjects. In these studies the underlying causative factor which produced a lengthening of the rapid filling phase with bleeding, as well as with the application of cuffs and with the assumption of the upright posture, appeared to be the production of a decreased atrioventricular pressure-filling gradient.

MITRAL VALVE LESIONS

A characteristic abnormality in the tracing recorded from the left auricle in cases of mitral valve disease has been described by Luisada and Fleischner,[21] who described a characteristic wave pattern in all cases of mitral valve disease whether of mitral insufficiency, mitral stenosis, or stenosis and insufficiency combined. The pattern appeared to be more marked in patients having coincident auricular fibrillation. Engström and associates,[44] Phillips,[25] Lian and Minot,[4] Soulie and associates,[64] and, more recently, McKinnon and Friedman[68] have confirmed this pattern in mitral disease.

The characteristic pattern found by these investigators (lower curve of Fig. 8), consists of a rectangular, positive plateau occurring during auricular diastole. The sharply rising limb of this curve is due to a regurgitant flow of blood from the left ventricle into the auricle because of the mitral valve insufficiency. The auricle remains engorged during its diastole and provides the plateau effect on the curve. The descending limb begins when the left ventricular relaxes and its pressure falls below the auricular pressure. The descending limb therefore results from auricular blood volume reduction, and reaches its lowest point in 0.14 to 0.16 second. Absence of an auricular contraction wave preceding this rectangular complex is also a feature of this abnormal electrocardiogram.

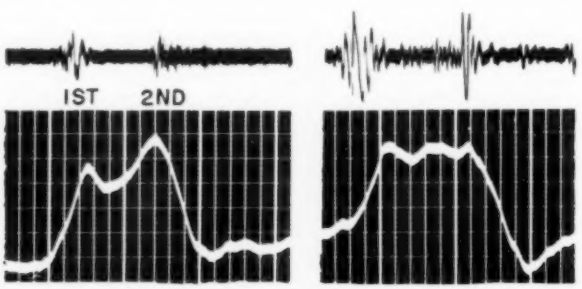

Fig. 8.—The lower curves are left auricular electrokymograms from two cases of mitral valve disease. Heart sounds are recorded on the upper curves. The sharp rising limb of auricular curves begins with the first heart sound and results from a regurgitant flow from the left ventricle. (See text. Compare with Figs. 2 and 3.)

Differentiation of this positive plateau of the left auricle must be made from the pulsations of the pulmonary artery and hilar vessels. This can be done by carefully observing the timing of the respective events, the arterial events occurring somewhat later in time.

AORTIC AND PULMONARY VALVE LESIONS

Electrokymographic studies of the aorta and pulmonary artery have been shown by Heyer, Poulos, and Acker[57] to exhibit certain alterations from the normal, in the presence of lesions of the aortic and pulmonic valves. Thus, in a group of twenty-two patients with clinical and physical findings characteristic of aortic insufficiency, electrokymographic tracings of the aorta revealed a definite and marked decrease in size of the incisura. This landmark, which indicates closure of the semilunar valves, was completely absent in some patients. In

others the incisura was a small vestigial remnant of the normal, and was found to be located far down on the descending limb of the aortic tracing (Fig. 9). It was also noted that in aortic insufficiency there was a more rapid fall of the descending limb of the aortic ejection curve, in early diastole, than is seen in normal tracings of the aorta. In some instances the ejection phase was also altered, showing an

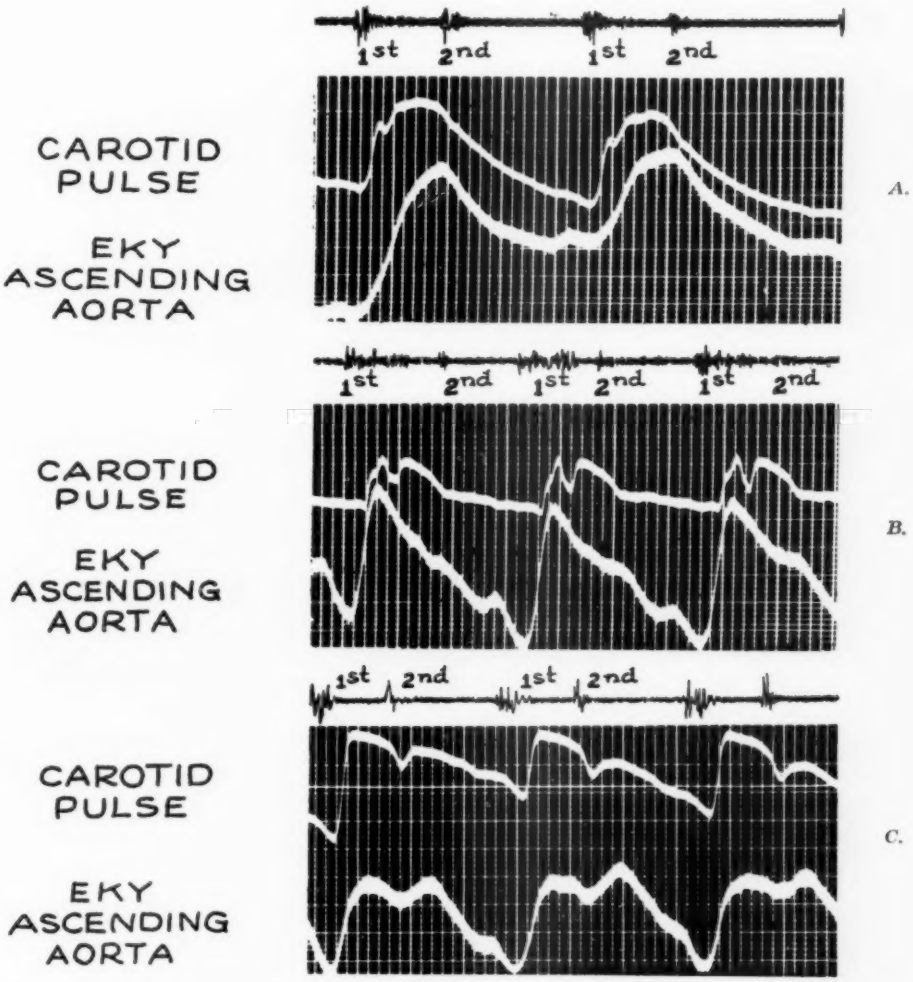

Fig. 9.—*A*, Electrokymographic tracing of ascending aorta in patient with aortic insufficiency. A Negro woman, age 51 years with loud blowing aortic diastolic murmur audible at primary and secondary aortic auscultatory areas. Marked cardiac enlargement, hyperactive peripheral vessels, and positive serologic test for syphilis. The significant feature here is the absence of any incisural or predicrotic notch. (Compare with tracing of normal aorta in *C*.) First and second heart sounds are indicated above carotid pulse.

B, Electrokymographic tracing of ascending aorta in patient with aortic insufficiency. The important features of this tracing are the rapidity of early ejection, with a sharp upsweep, and the almost complete lack of an incisura, this being seen only as a small vestigial marking on the downsweep of the tracing. Patient had loud blowing diastolic murmur at left sternal border with marked cardiac enlargement and Corrigan type pulse. Serologic tests positive for syphilis.

C, Electrokymograph of ascending aorta of normal healthy adult. Note presence of well-defined predicrotic notch, or incisura, indicating closure of the aortic valve. There is a moderately rapid upswing of the tracing in the early phase of ejection.

abrupt and sharp discharge of blood into the aorta in the early phases of the systole. Moreover, the total duration of the ejection phase was prolonged in patients with aortic insufficiency, as compared to normal subjects. From a physiologic standpoint it is probable that the increased amount of blood expelled from the ventricle with this type of valvular lesion, as well as the magnitude of the regurgitant leak, are factors of great importance in producing the alterations noted. These findings were present in aortic insufficiency due to syphilis as well as rheumatic endocarditis.

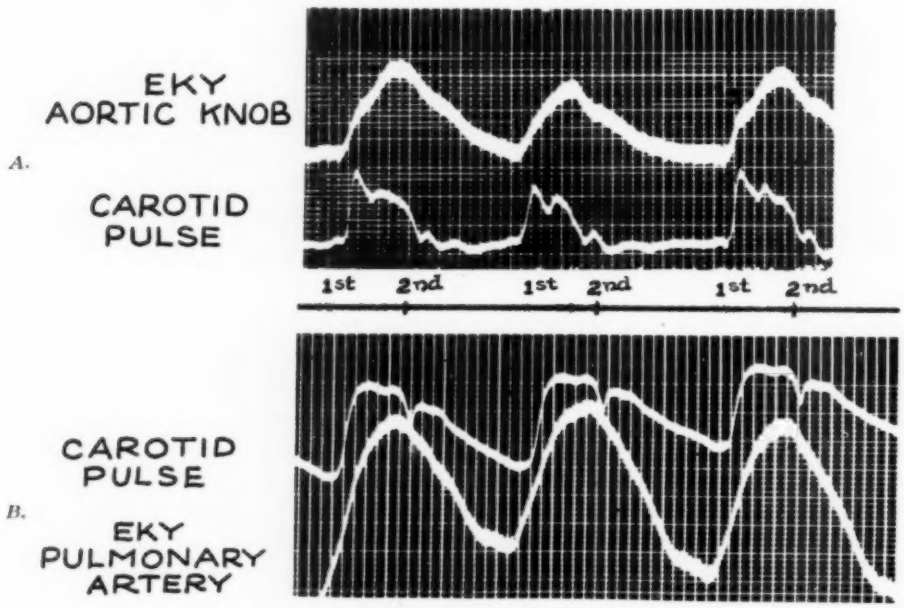

Fig. 10.—*A*, Rheumatic heart disease with aortic stenosis and insufficiency; electrokymograph of ascending aorta. Following initial rapid upsweep of tracing, in early ejection, there is a well-marked change in gradient of curve with more gradual upsweep in curve to summit. There is a poorly defined incisural (predicrotic) notch on descending limb of tracing. Patient was elderly white woman with history of rheumatic fever in childhood, with loud, harsh systolic murmur at first right intercostal space, also audible in neck. Blowing diastolic murmur at primary aortic area and left sternal border. Serologic test for syphilis negative. The presence of this anacrotic notch on the upswing is characteristic of aortic stenosis, as is the decreased or absent predicrotic notch in aortic insufficiency.

B, Pulmonary insufficiency, complicating tetralogy of Fallot in cyanotic patient. Electrokymographic tracing of pulmonary artery shows complete absence of incisura, while similar tracing of aorta (not shown here) revealed well-defined predicrotic notch. Patient had poststenotic dilatation of pulmonary artery with pulmonary insufficiency. Loud, blowing diastolic murmur at third left intercostal space with harsh systolic murmur in same area. By utilizing electrokymographic tracings of both large vessels, it is thus possible to determine the site of origin of doubtful left sternal border murmers.

In one instance of congenital pulmonary artery disease, with clinical findings of pulmonary insufficiency, the incisura was found to be completely absent in tracings of the pulmonary artery (Fig. 10, lower tracing). This patient exhibited a loud blowing diastolic murmur at the second left intercostal space, compatible with insufficiency of the pulmonic valve. Thus, it would appear possible, by taking tracings of the pulmonic artery and aorta, to determine whether the source of a blowing diastolic left sternal border murmur originated in a defect of the aortic or of the pulmonic valve.

In the same study, two patients with definite evidence of aortic stenosis revealed distinct alterations from the normal in tracings of the ascending aorta. The rapid ejection phase was divided into two separate phases; a rapid upswing ending abruptly in a much slower upward rise (Fig. 10, upper tracing). This is actually an exaggeration of the normal anacrotic inflection which is present in normal subjects. Similar findings have been recorded by Feil,[103] from tracings of the subclavian pulse, in patients with aortic stenosis.

STUDIES ON ASYNCHRONISM

Speculation on the synchronous or asynchronous contraction of the two sides of the heart has long concerned investigators. That the two sides of the normal heart do not necessarily contract simultaneously was shown early by Stassen,[92] Fauconnier,[93] Eppinger and Rothberger,[94,95] and later by Katz.[96] Katz demonstrated, by pressure-recording methods, that in normal dogs ejection of blood from the ventricles was not synchronous in most cases. He did not, however, suggest that electrical asynchronism was responsible. Wiggers and Banus[97] studied electrical and mechanical phenomena in normal ventricles and concluded that the two ventricles were independent in that the two phenomena are not necessarily correlated.

Wolferth, Margolies, and Bellet,[98] and Wolferth and Margolies,[99] studying patients with left bundle branch block, concluded that correlation between the electrical and mechanical phases of the cardiac cycle did occur. Later work of Katz and his associates[100] did not corroborate these findings. Battro and associates[101] concluded that ". . . the electrocardiogram by itself is not a reliable means for establishing the diagnosis of complete bundle branch block with its mechanical consequences." They further indicated that only the adequate recording of the mechanical events of the heart could afford a means of determining the existence of ventricular asynchronism.

With the development of the electrokymograph a new technique became available for the study of this problem. The mechanical motions of the borders of the heart and great vessels in man could now be simultaneously recorded with other mechanical events and with the electrical events. Ellinger and associates[16] utilized this new technique to study the synchronism or asynchronism of ventricular ejection in sixty-eight normal adults and sixteen patients with bundle branch block. Their method was based on determining the time interval between the onset of the ejection on the pulmonary artery electrokymograph and that of the ascending aorta. For practical purposes this indicates the time of onset of ejection of blood from the right ventricle relative to that from the left ventricle. They found in a group of sixty-eight normal persons that left ventricular ejection preceded the right in thirty-three cases; right ventricular ejection preceded in twenty-one cases, and ejection was synchronous in fourteen cases. Ejection from either ventricle may normally precede that from the other by 0.03 second or less. In six patients with right bundle branch block, right ventricular ejection followed the left in every case by 0.04 second or more; and in nine of ten patients with left bundle branch block, the right ventricular ejection preceded the left by 0.04 to 0.07 second. It appears from this that mechanical asynchronism is a normal

occurrence and that increased amounts of mechanical asynchronism may be associated with the presence of bundle branch block.

Luisada and Fleischner[12] studied eight normal subjects by electrokymographic methods and found mechanical asynchronism to occur. In all observations they found the contraction of the right auricle to precede the left auricle and the contraction of the right ventricle to precede the left ventricle. The delay of the left chambers was between 0.025 to 0.03 second.

Samet and associates[59] likewise employed this new technique to study the correlation of electrical and mechanical asynchronism in the cardiac cycle. Simultaneous electrokymograms from the ascending aorta and the pulmonary artery were recorded with electrocardiograms. Eighty-three cases of bundle branch block were studied. In 70 per cent of the cases they failed to find mechanical asynchronism accompanying the electrical asynchronism. They did find, however, evidence in a majority of cases of delayed ejection from both ventricles. This finding, it is suggested, may be related to post-mortem examinations, where lesions in both bundle branches are found more commonly than in one bundle.

EFFECT OF DIGITALIS

Careful serial studies were made by Eddleman and associates[104] of the contour and duration of the various phases of the cardiac cycle after the administration of a dose of 2 mg. digitoxin (in a twelve-hour period) to normal subjects. The significant findings noted were: (1) a fall in cardiac output (measured by a modification of the method of Ring and his associates, utilizing the electrokymograph) reaching its lowest point eight to forty-eight hours after the administration of digitoxin; (2) a fall in stroke volume during the same period; (3) an increase in the rapidity of ejection of blood from the heart, including a more rapid upsweep of the ejection curve obtained from electrokymographic tracings of the aorta; (4) a decrease in heart size, in both systole and diastole, as indicated by a decrease in the posterior-anterior diameters; and (5) a definite slowing of the rate of ventricular diastolic filling, as indicated by a lengthening of the duration of the rapid-filling phase.

The increased rapidity of ejection of blood and the decreased heart size were ascribed by these authors to a direct cardiotonic effect, causing increased cardiac emptying. The fall in stroke volume and cardiac output were considered to be due to (1) an early increase in peripheral resistance, in the earliest phases of digitalization, in some subjects, and (2) to a diminished venous return to the heart, as measured by a slow and prolonged rate of early ventricular diastolic filling, evident in all subjects studied. This slowing in the rate of ventricular filling was thought to be due to a peripheral effect of digitalis on the venous system, with venous constriction and a diminished volume of blood returning to the heart.

STUDIES IN CARDIAC OUTPUT

An interesting and what may prove one of the most important applications of electrokymography was first proposed by Ring, Balaban, and Oppenheimer[36] and further applied by Eddleman, Willis, and Heyer.[73,74]

Ring and associates[36] conducted studies in which the amplitude of electrokymograms (densograms) taken over the body of the left ventricle were correlated to the cardiac output. A small presswood (masonite) vane (calibrator) of certain x-ray opacity was passed quickly and repeatedly through the x-ray beam while (1) a density electrokymograph of the chest just to one side of the heart was taken; and (2) a density electrokymograph through the left ventricle and chest was taken. The calibrating wave was timed to occur precisely at the end of systolic ejection. From the difference of amplitudes of the calibrating wave through the chest and through the chest and heart, they calculated the systolic anteroposterior thickness of the heart. Next, a comparison of the amplitude of the calibration wave taken through the heart at end of systole, to the amplitude of the ventricular electrokymographic curve, permitted them to calculate the diastolic thickness of the ventricle. The difference between the systolic and diastolic ventricular thickness is related to stroke volume. A formula was developed to translate this thickness value into volume terms.

Continuing their work, Ring and associates[61,62] studied the correlation between their electrokymographic output measurements to outputs measured by the Fick and the Stewart principles. In their entire group of measurements, they reported only 12 per cent of the electrokymographic determinations differed more than 25 per cent from the other methods of determining cardiac output.

In utilizing this technique for measuring cardiac output with the electrokymograph, numerous variables are apparent. An important one relates to the optimum site on the left ventricle from which output measurements should be taken. Rudel and associates[54] and Ring and associates[75,81] have reported on this quite extensively.

Eddleman, Willis, and Heyer,[73] with certain modifications of Ring's method, utilized the electrokymographic technique principally to determine directional changes, that is, increase or decrease of stroke volume in studying the mechanics of postural adaptation in normal young adults. Among their findings there occurred an average of 38 per cent reduction of stroke volume together with a shortened period of total systole and of ejection phase during a change from supine to vertical position. A direct correlation occurred between the duration of total systole and apparent stroke volume.

In further studies, on prolonged motionless standing, Eddleman, Willis, and Heyer[74] noted three phases of physiologic response. First, a decrease in stroke volume occurred during the initial four to twelve minutes; second, a temporary rise of stroke volume followed, and third, a continued decrease of stroke volume took place until syncope ensued.

STUDIES IN CONSTRICTIVE PERICARDITIS, INTRATHORACIC MASSES, AND MYOCARDIAL INFARCTION

Stumpf and associates[1] and Berner[102] utilizing roentgenokymograms pointed to a diastolic plateau as a characteristic feature in constrictive pericarditis. Berner described this as a "flattop and V" pattern. Gillick and Reynolds[22,39] were the first

to report a similar pattern using the electrokymograph. The characteristics of this "flattop and V" ventricular electrokymographic pattern (Fig. 11) are: (1) secondary waves of the normal ventricular curve are absent; (2) the downward limb of the V wave occurs during ejection phase; (3) the rising limb of the V wave occurs during rapid diastolic filling, and (4) the flattop portion occurs during the remainder of diastole (Fig. 11). McKusick,[82,84,106] reporting twenty cases, found this electrokymographic pattern "highly" diagnostic of chronic adhesive pericarditis, and a valuable index of results of pericardectomy. Paley and Dack[85] in several instances observed practically absent contractile movements over the ventricular border, which returned to normal after operation.

Gillick and Reynolds[22] suggested a method, utilizing the electrokymograph, to differentiate intrathoracic tumor masses from aneurysms. They found an experimental aneurysm to expand synchronously with the vessel in all border and density positions, while on an experimental tumor mass one border moved synchronous to the vessel as the opposite border moved oppositely on the record.

In the study and diagnosis of myocardial infarction, electrokymography has attained perhaps one of its best practical clinical applications.[24,34,41,55,88] Dack and Paley[88] have recently reviewed this application comprehensively. The abnormalities of the ventricular movement may be visible during the systolic and diastolic phases of the cycle. Abnormalities during the systolic phase may be classified in three main groups: (1) localized diminution or absence of motion; (2) partial reversal of pulsation, and (3) complete reversal or sustained outward ventricular movement during entire systole. The abnormalities during the diastolic phase may be: (1) mesial movement in early diasole; (2) retarded or absent filling, and (3) complete reversal of pulsation or sustained inward movement throughout diastole. Fig. 12 illustrates left ventricular electrokymograms from four cases of myocardial infarction and shows complete reversal of pulsations in each case. The sharp rising limb just prior to the carotid curve take-off results from isometric systolic expansion. The following systolic plateau lasts through systole, and the sharp downward limb results from diastolic collapse. Curve *D* in addition shows a mechanical alternans, though no electrocardiographic electrical alternans was present.

STUDIES IN CONGESTIVE FAILURE

In the presence of nonvalvular congestive failure (without digitalis) Heyer and associates[105] found that the duration of the rapid-filling phase appeared to be definitely shortened when compared with normal subjects (Fig. 13). This shortening of the rapid-filling phase was apparently not related to changes in heart rate. It appeared most likely that the increased rapidity of ventricular filling was related to the presence of an increased pressure-filling gradient between auricle and ventricle, which was present in the failing heart in the very earliest phases of ventricular diastole. It is interesting to note that this increased rapidity of filling appeared under clinical conditions most frequently associated with the development of a diastolic gallop sound in heart failure. Irrespective of the exact mode of origin of the gallop sound—whether it be valvular or non-

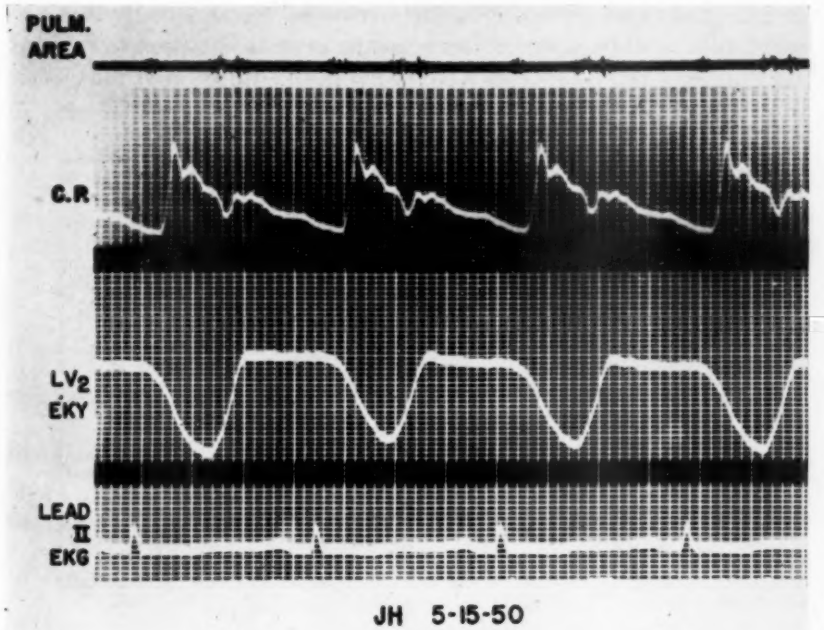

Fig. 11.

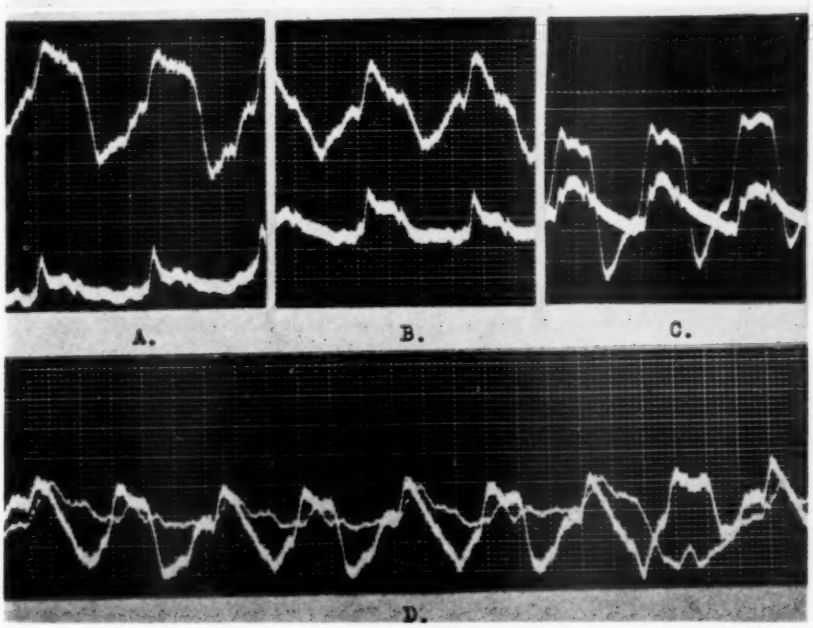

Fig. 12.

Fig. 11.—An electrokymogram in chronic constrictive pericarditis. Heart sounds are on the upper curve, carotid pulse on the second curve, left ventricular electrokymograph (*EKY*) on the third curve, and electrocardiogram on the bottom curve. The electrokymogram curve shows the typical flattop and "V" pattern described in the text.

Fig. 12.—Records *A*, *B*, *C*, and *D* are from four cases of left ventricular infarction. The upper curves are electrokymograms, the lower curves are carotid pulse. Each electrokymograph curve shows the abnormal systolic expansion during ventricular systole and the following diastolic collapse. Curve *D* also exhibits mechanical alternans.

valvular in origin—the rapid entrance of the stream of blood into the ventricle in diastole would appear to be a major factor in the genesis of gallop sounds. In the same studies, no significant changes were noted in the duration of the ejection phase or of total systole in the presence of congestive heart failure.

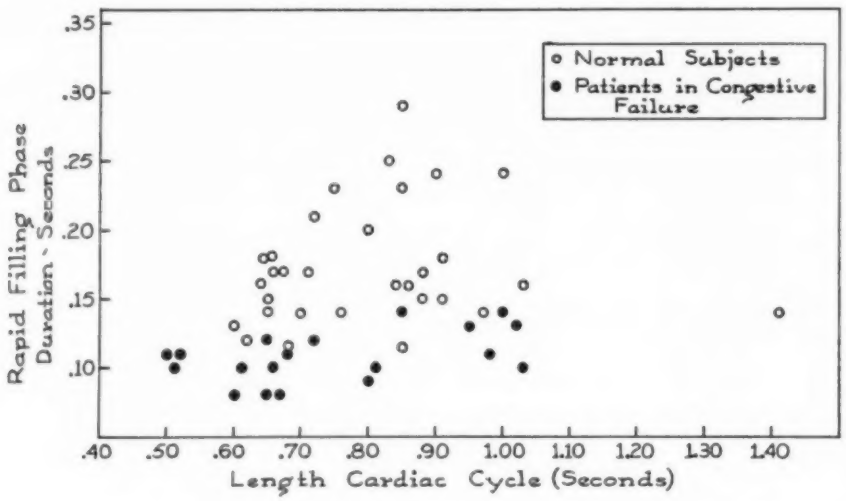

Fig. 13.—Duration of rapid filling in patients in congestive failure and in normal subjects, determined from the left ventricle. It will be noted that, as a group, the patients in congestive failure have a shorter rapid-filling phase than the normal subjects.

SUMMARY

The development of the electrokymograph has made it possible to record heart border motion, as well as changes in cardiac density, with accuracy and comparative ease. The instrument possesses dual potentialities as both a diagnostic clinical aid and a physiologic tool. Thus, it has provided additional diagnostic help in patients with myocardial infarction, valvular lesions, and pericarditis. In the field of physiologic research it has yielded valuable data concerncerning the timing and duration of the various phases of the cardiac cycle, the occurrence of asynchronism of cardiac chambers, as well as the effect of posture, hemorrhage, and digitalis, on the cardiac cycle. It has also been useful in studying variations in cardiac activity in the presence of congestive failure, and has provided another means of measuring cardiac output. It therefore has a wide field of application in clinical cardiology and physiology. Future experience with the electrokymograph will probably add further information concerning its usefulness as well as its limitations.

REFERENCES

1. Stumpf, P., Weber, H. H., and Weltz, G. A.: Roentgenkymographische Bewegungslehre Inner Organe, Leipzig, 1936, Georg Thieme.
   Stumpf, P.: Kymographische Roentgendiagnostik zur Beurteilung des Herzens, Stuttgart, 1951, Georg Thieme.
2. Henny, G. C., and Boone, B. R.: Electrokymograph for Recording Heart Motion Utilizing the Roentgenoscope, Am. J. Roentgenol. **54**:217, 1945.
3. Boone, B. R., Gillick, F. G., Chamberlain, W. E., and Oppenheimer, M. J.: Electrokymograms of Heart Border Motions; Principles of Record Interpretation, Federation Proc. **5**:9, 1946.

4. Lian, C., and Minot, G.: La radioelectrokymographie, Arch. d. mal. du coeur **39**:339, 1946.
5. Gillick, F. G., Boone, B. R., Henny, G. C., and Oppenheimer, M. J.: The Electrokymograph; Application as a Photo-Electric Plethysmograph, Federation Proc. **5**:33, 1946.
6. Henny, G. C., Boone, B. R., and Chamberlain, W. E.: The Electrokymograph: An Apparatus for Recording Motion (For Example, That of the Heart Border Shadow), Federation Proc. **5**:44, 1946.
7. Henny, G. C., Boone, B. R., and Chamberlain, W. E.: Electrokymograph for Recording Heart Motion, Improved Type, Am. J. Roentgenol. **57**:409, 1947.
8. Chamberlain, W. E., Boone, B. R., Ellinger, G. F., Henny, G. C., and Oppenheimer, M. J.: Asynchronism of Ejection of the Ventricles as Measured With the Electrokymogram, Federation Proc. **6**:88, 1947.
9. Chamberlain, W. E.: Roentgen Elektrokymography, Acta radiol. **28**:847, 1947.
10. Stauffer, H. M.: Electrokymography, Univ. Minnesota Staff Meeting Bull. **18**:462, 1947.
11. Sussman, M. L.: A Physiologic Approach to Cardiovascular Roentgenology, Minnesota Med. **30**:1041, 1947.
12. Luisada, A. A., and Fleischner, F. G.: Temporal Relation Between Contraction of Right and Left Sides of the Normal Human Heart, Proc. Soc. Exper. Biol. & Med. **66**:436, 1947.
13. Boone, B. R.: Application of the Electrokymograph to the Study of Cardiovascular Physiology, Abstract of Communications, XVII, International Physiological Congress 6, Oxford, 1947.
14. Henny, G. C.: Electrokymograph: Apparatus for Recording Cardiovascular Phenomena Utilizing the Roentgenoscope, Abstract of Communications, XVII, International Physiological Congress 5, Oxford, 1947.
15. Boone, B. R., Chamberlain, W. E., Gillick, F. G., Henny, G. C., and Oppenheimer, M. J.: Interpreting the Electrokymogram of Heart and Great Vessel Motion, Am. Heart J. **34**:560, 1947.
16. Ellinger, G. F., Gillick, F. G., Boone, B. R., and Chamberlain, W. E.: Electrokymographic Studies of Asynchronism of Ejection From the Ventricles, Am. Heart J. **35**:971, 1948.
17. Boone, B. R., Randak, E. F., Ellinger, G. F., and Oppenheimer, M. J.: Electrokymographic Studies of the Ventricular Isometric Relaxation Phase of the Cardiac Cycle in Man, J. Appl. Physiol. **1**:534, 1949.
18. Luisada, A. A., Fleischner, F. G., and Rappaport, M. B.: Fluorocardiography (Electrokymography). I. Technical Aspects, Am. Heart J. **35**:336, 1948.
19. Luisada, A. A., Fleischner, F. G., and Rappaport, M. B.: Fluorocardiography (Electrokymography). II. Observations on Normal Subjects, Am. Heart J. **35**:348, 1948.
20. Fleischner, F. G., Romano, F. J., and Luisada, A. A.: Studies of Fluorocardiography in Normal Subjects, Proc. Soc. Exper. Biol. & Med. **67**:535, 1948.
21. Luisada, A. A., and Fleischner, F. G.: Dynamics of the Left Auricle in Mitral Valve Lesions, Am. J. Med. **4**:791, 1948.
22. Gillick, F. G., and Reynolds, W. F.: Clinical Application of Electrokymography, California Med. **70**:407, 1949.
23. Schneider, J., and Gillick, F. G.: Elektrokymographie, Cardiologia Separatum XIV: Fasc. 1/2, 1949.
24. Sussman, M. L., Dack, S., and Paley, D. H.: Some Clinical Applications of Electrokymography, Radiology **53**:500, 1949.
25. Phillips, E.: The Electrokymogram in Valvular Heart Disease, Permanente Found. M. Bull. **7**:25, 1949.
26. Lewis, J. L., Jr., and Terry, L. L.: Electrokymography—An Appraisal of Its Present Clinical Status, Ann. Int. Med. **32**:36, 1950.
27. Oppenheimer, M. J., and Chamberlain, W. E.: Roentgen Electrokymograph, Methods in Medical Research 1, Chicago, 1948, The Yearbook Publishers, Inc., p. 232.
28. Luisada, A. A.: La Fluorocardiografia; methodica, osservazioni, fisiologiche, studi clinici, Cuore e circolaz. **32**:125, 1948.
29. Randak, E. F., Boone, B. R., Ellinger, G. F., and Oppenheimer, M. J.: Ventricular Isometric Relaxation Phase as Measured on the Electrokymogram, Federation Proc. **7**:97, 1948.
30. Luisada, A. A., and Fleischner, F. G.: Studies of Flurocardiography: Tracings of the Left Ventricle in Myocardial Infarction, Acta cardiol. **4**:308, 1948.
31. Luisada, A. A., Romano, F. J., and Torre, J. M.: Isometric Relaxation Period of the Left Ventricle in Normal Subjects and Patients With Mitral Stenosis, Proc. Soc. Exper. Biol. & Med. **69**:23, 1948.

32. Kay, C. F., Woods, J. W., Jr., Zinsser, H. F., Jr., and Benjamin, J. M., Jr.: The Validity of the Electrokymographic Method for Measurement of Diameter Change of the Aorta and Pulmonary Artery During Circulatory Disturbance, J. Clin. Investigation **28**:228, 1949.
33. Stauffer, H. M., and Jorgens, J.: Electrokymography of the Heart and Great Vessels, Radiology **52**:488, 1949.
34. Boone, B. R., Ellinger, G. F., and Gillick, F. G.: Electrokymography of the Heart and Great Vessels, Principles and Application, Ann. Int. Med. **31**:1030, 1949.
35. Luisada, A. A., and Fleischner, F. G.: Fluorocardiography (Electrokymography), Am. J. Med. **6**:756, 1949.
36. Ring, G. C., Balaban, M., and Oppenheimer, M. J.: Measurements of Heart Output by Electrokymography, Am. J. Physiol. **157**:343, 1949.
37. Ring, G. C., Michie, C. R., and Oppenheimer, M. J.: Starling's Law and X-ray Density Changes of Heart Shadow, Am. J. Physiol. **156**:339, 1949.
38. Luisada, A. A., and Fleischner, F. G.: Simultaneous Fluorocardiography and Recording of Intracardiac Pressure, Proc. Soc. Exper. Biol. & Med. **70**:730, 1949.
39. Gillick, F. G., and Reynolds, W. F.: Electrokymographic Observations in Constrictive Pericarditis, Radiology **55**:77, 1950.
40. Gillick, F. G., and Schneider, J.: Electrokymographic Studies of Lung Field Pulsations With Exhalation Against Pressure, J. Appl. Physiol. **2**:30, 1949.
41. Gillick, F. G., and Schneider, J.: Abnormal Electrokymograms From the Wall of the Ventricle With and Without Evidence of Myocardial Infarction, Am. J. M. Sc. **219**:500, 1950.
42. Dussaillant, G., Lepe, A., and del Fierro, M.: Electrokymography, Rev. méd. de Chile **77**:307, 1949.
43. Grossman, N., and Tiger, E.: A New Mounting for the Electrokymograph, J. Lab. & Clin. Med. **34**:1298, 1949.
44. Engstrom, B., Kjellberg, S. R., Persson, L., and Rudhe, U.: Some Aspects of Use of Electrokymography in Cardiac Investigations, Acta radiol. **31**:435, 1949.
45. Morgan, R. H.: Electrokymography, Am. J. M. Sc. **218**:587, 1949.
46. Hjalmare, G.: Registration of Movements of the Heart With Geiger-Muller Counters and Synchronous Electrocardiography, Acta radiol. **27**:334, 1946.
47. Marchal, M.: De l'enregistrement des pulsations invisibles du parenchyme pulmonaire ainsi que des pulsations cardiovasculaires par la kinedensigraphie, Arch. d. mal. du coeur. **39**:345, 1946.
48. Andersson, T.: Electrokymography With Simultaneous Electrocardiography, Acta radiol. **30**:36, 1948.
49. Luisada, A. A., and Fleischner, F. G.: Fluorocardiography (Electrokymography) During Normal Respiration, Proc. Soc. Exper. Biol. & Med. **72**:155, 1949.
50. Posteli, T.: Studii di elettrochimografia, Estratto da Radioterapia, Radiobiologia e Fisica Medica **2**:112, 1949.
51. Jorgens, J., LaBree, J. W., Adams, F. H., and Veasy, L. G.: An Electrokymographic Study of the Pulmonary Pulsations in Congenital Heart Disease, Bull. Univ. Minn. Hospitals & Minn. Med. Found. **21**:243, 1950.
52. Clagett, A. H.: The Electrokymogram in Angina Pectoris, Delaware State M. J. **22**:44, 1950.
53. Zinsser, H. F., and Kay, C. F.: The Straining Procedure as an Aid in the Anatomic Localization of Cardiovascular Murmurs and Sounds, Circulation **1**:523, 1950.
54. Rudel, H. W., Sokalchuk, A., Ring, G. C., and Navis, G. J.: Movements of the Dog's Heart in the Closed Chest, Federation Proc. **9**:111, 1950.
55. Dack, S., Paley, D. H., and Sussman, M. L.: A Comparison of Electrokymography and Roentgenkymography in the Study of Myocardial Infarction, Circulation **1**:551, 1950.
56. Dack, S., Paley, D. H., and Brahms, S. S.: Ventricular Contraction in Wolff-Parkinson-White Syndrome: An Electrokymographic Study, Bull. New York Acad. Med. **26**:273, 1950.
57. Heyer, H. E., Poulos, E., and Acker, J. H.: Electrokymographic Studies in Insufficiency of the Aortic and Pulmonic Valves, Circulation **1**:1037, 1950.
58. Samet, P., Schwedel, J. B., and Mednick, H.: Electrokymographic Studies in Aneurysm of the Left Ventricle, AM. HEART J. **39**:749, 1950.
59. Samet, P., Mednick, H., and Schwedel, J. B.: Electrokymographic Studies of the Relationship Between Electrical and Mechanical Asynchronism in the Cardiac Cycle, AM. HEART J. **39**:841, 1950.
60. Mednick, H., Schwedel, J. B., and Samet, P.: Electrokymographic Studies of the Normal Cardiac Cycle, Circulation **2**:250, 1950.
61. Ring, G. C., Greisheimer, E. M., Baier, H. N., Oppenheimer, M. H., Sokalchuk, A., Ellis, D., and Friday, S. J.: Electrokymograph for Estimation of Heart Output: Comparison With Direct Fick in Dogs, Am. J. Physiol. **161**:231, 1950.

62. Ring, G. C., Sokalchuk, A., Baier, N. H., Rudel, H., Oppenheimer, M. J., Friday, S. J., and Navis, G.: Electrokymograph for Estimation of Heart Output: Comparison With Stewart in Dogs, Am. J. Physiol. **161**:236, 1950.
63. Brady, J. P., and Taubman, F.: The Anomalous Motion of the Heart Border in Subjects With Gallop Rhythm or Third Heart Sounds, AM. HEART J. **39**:834, 1950.
64. Soulie, P., Di Matteo, J., and Marchal, M.: La cinedensigraphie dans les valvulites mitrales. Regurgitation systolique auriculaire, Arch. d. mal. du coeur **43**:14, 1950.
65. Schwedel, J. B., Samet, P., and Mednick, H.: Electrokymographic Studies of the Relationship Between Electrical and Mechanical Events of the Cardiac Cycle, Proc. Soc. Exper. Biol. & Med. **73**:591, 1950.
66. Zinsser, H. F., Kay, C. F., and Benjamin, J. M., Jr.: The Electrokymograph: Studies in Recording Fidelity, Circulation **2**:197, 1950.
67. Luisada, A. A., and Fleischner, F. G.: Attempts at Clinical Measurement of Pulmonary Arterial Pressure, Exper. Med. & Surg. **8**:251, 1950.
68. McKinnon, J. B., and Friedman, B.: Electrokymographic Studies of the Left Atrium in Normal and Diseased Hearts, Circulation **2**:572, 1950.
69. Schwedel, J. B., Samet, P., and Mednick, H.: Electrokymographic Studies of Abnormal Left Ventricular Pulsations, AM. HEART J. **40**:410, 1950.
70. Samet, P., Mednick, H., and Schwedel, J. B.: Electrokymographic Studies of the Relation Between the Electrical and Mechanical Events of the Cardiac Cycle in Wolff-Parkinson-White Syndrome, AM. HEART J. **40**:430, 1950.
71. Sjostrand, T.: The Function of the Lungs as a Blood Reservoir and the Importance Thereof in the Regulation of the Circulation in Man, XVIII International Physiological Congress, Copenhagen, 1950.
72. Willis, K., Eddleman, E. E., Jr., Acker, J. K., Poulos, E., and Heyer, H. E.: Variations in the Duration of Phases of the Cardiac Cycle in Normal Hearts as Studied by the Electrokymograph, AM. HEART J. **40**:485, 1950.
73. Eddleman, E. E., Jr., Willis, K., and Heyer, H. E.: The Effect of Posture on the Cardiac Cycle, Posteroanterior Cardiac Diameters, and Apparent Stroke Volume as Studied by the Electrokymograph, AM. HEART J. **40**:504, 1950.
74. Eddleman, E. E., Jr., Willis, K., and Heyer, H. E.: The Effect of Prolonged Motionless Standing on the Phases of the Cardiac Cycle, Stroke Volumes, and the Posteroanterior Diameters of the Heart as Studied by the Electrokymograph, J. Appl. Physiol. **4**:156, 1951.
75. Ring, G. C., Sokalchuk, A., Navis, G. J., and Rudel, H. W.: Positional Changes of the Heart and Their Effects on Electrokymographic Recordings, Am. J. Physiol. **163**:468, 1950.
76. Akman, L. C., Miller, A. J., Silber, E. N., Schack, J. A., and Katz, L. N.: The Ventricular Electrokymogram, Circulation **2**:890, 1950.
77. Salans, A. H., Schack, J. A., and Katz, L. N.: Correlation of Simultaneously Recorded Electrokymograms and Pressure Pulses of Human Heart and Great Vessels (a Preliminary Report), Circulation **2**:900, 1950.
78. Dack, S., Paley, D. H., and Brahms, S. S.: The Electrokymogram in Wolff-Parkinson-White Syndrome, AM. HEART J. **41**:437, 1951.
79. Phillips, Edward: Electrokymographic Studies of Ventricular Border Movements in Aortic Insufficiency and Ventricular Hypertrophy, Ann. West. Med. & Surg. **5**:536, 1951.
80. Andersson, T.: Electrokymographic Recording of Auricular Movements, Acta radiol. **32**:121, 1949.
81. Electrokymography. Proceedings of the First Conference on Electrokymography, 1950. Public Health Service Publication No. 59, Washington, D. C., United States Government Printing Office, 1951.
82. Salans, A. H., Katz, L. N., Graham, G. R., Gordon, A., Elisberg, E. I., and Gerber, A.: A Study of the Central and Peripheral Arterial Pressure Pulse in Man, Circulation **4**:510, 1951.
83. Morgan, Russell H.: The Quantitative Electrokymograph, Circulation **4**:604, 1951.
84. McKusick, V. A.: Chronic Constrictive Pericarditis. I. Some Clinical and Laboratory Observations, Bull. Johns Hopkins Hosp. **90**:3, 1952.
85. Paley, D. H., and Dack, S.: The Electrokymogram in Constrictive Pericarditis. To be published.
86. Dack, S., and Paley, D. H.: Electrokymography. I. The Ventricular Electrokymogram, Am. J. Med. **12**:331, 1952.
87. Paley, D. H., and Dack, S.: Electrokymographic Studies of the Isometric Relaxation Phase. To be published.
88. Heckmann, Karl: Die Untersuchung der Herzpulsation mittels der Elektrokymographie und Phasenanalyse, Ztschr. f. Kreislaufforsch. **41**:1, 1952.
89. Jacobi, J., Janker, R., and Schmitz, W.: Combination of X-ray Cinematographic, Ionometric and Electrocardiographic Investigations, Deutsches Arch. f. klin. Med. **172**:493, 1932.

90. Heckmann, Karl: Graphic Presentation of the Changes in Brightness of the Image of the Heart on the Fluorescent Screen (Actinocardiogram) in Mitral Insufficiencies, Klin. Wchnschr. **15**:928, 1936.
91. Heckmann, Karl: Modern Methods for Investigation of Heart Pulsation by Means of X-rays, Ergebn. d. inn. Med. u. Kinderh. **52**:543, 1937.
92. Stassen, M.: De l'ordre de succession des differentes phases de la pulsation cardioque chez le chien, Arch. internat. de physiol. **5**:60, 1907.
93. Fauconnier, H.: Sur l'onde de contraction de la systole ventriculaire, Arch. internat. de physiol. **7**:462, 1908-1909.
94. Eppinger, H., and Rothberger, J.: Ueber die Folgen der Tawaraschen Schenkel des Reizleitungssytems, Ztschr. f. klin. Med. **70**:1, 1910.
95. Eppinger, H., and Rothberger, J.: Ueber die Sukzession der Kontraktion der beiden Herzkammern, Zentralbl. f. Physiol. **24**:1053, 1910.
96. Katz, L. N.: The Asynchronism of Right and Left Ventricular Contraction and the Independent Variations in Their Duration, Am. J. Physiol. **72**:655, 1925.
97. Wiggers, C. J., and Banus, M. G.: On the Independence of Electrical and Mechanical Activity in the Mammalian Ventricle, Am. J. Physiol. **76**:215, 1926.
98. Wolferth, C. C., Margolies, A., and Bellet, S.: The Side of the Significant Lesion in the Common Type of Bundle Branch Block, Tr. A. Am. Physicians **48**:187, 1933.
99. Wolferth, C. C., and Margolies, A.: Asynchronism in Contraction of the Ventricles in the So-called Common Type of Bundle Branch Block, Am. Heart J. **10**:425, 1935.
100. Katz, L. N., Landt, H., and Bohning, A.: The Delay in Onset of Ejection of the Left Ventricle in Bundle Branch Block, Am. Heart J. **10**:681, 1935.
101. Battro, A., Braun-Menendez, E., and Orias, O.: Asincronismo de la Contraccion Ventricular en la Bloqueo de Rama, Rev. argent. de cardiol. **3**:325, 1936.
102. Berner, F.: Die Kymographische Untersuchung der Pericarditis calculosa, Arch. f. klin. Chir. **194**:458, 1939.
103. Feil, H. S.: Subclavian Pulse in Aortic Valve Disease, Am. Heart J. **6**:778, 1930.
104. Eddleman, E. E., Willis, K., Greve, Marion J., and Heyer, H. E.: The Effect of Digitoxin on the Apparent Stroke Volume, Posteroanterior Cardiac Diameter, and the Cardiac Cycle in Normal Subjects as Studied by the Electrokymograph, Am. Heart J. **41**:161, 1951.
105. Heyer, H. E., Howard, C. H., Willis, K. W., and Pickle, A. C.: Alterations of the Rapid Filling Phase in Congestive Heart Failure, Am. Heart J. **43**:206, 1952.
106. McKusick, V. A.: Chronic Constrictive Pericarditis. II. Electrokymographic Studies and Correlations With Roentgenkymography, Phonocardiography, and Right Ventricular Pressure Curves, Bull. Johns Hopkins Hosp. **90**:27, 1952.

Book Review

ACCELERATED CONDUCTION. THE WOLFF-PARKINSON-WHITE SYNDROME AND RELATED CONDITIONS. By Prinzmetal, M., Kennamer, R., Corday, E., Osborne, J. A., Fields, J., and Smith, L. A. New York, 1952, Grune & Stratton, Inc., 110 pages, 48 figures.

The principal merit of this monograph is the abundant experimental material which the authors present. The tracings obtained for short P-R interval and aberrant ventricular responses are satisfactory and it is well to consider them as characteristic of Wolff-Parkinson-White syndrome.

The theoretical discussion is good, although many essential points are overlooked.

The authors do not discuss the theory of one or several ectopic foci in relation to electrotonic variations which originate in the auricle. All the experimental facts given by them are in agreement with this theory. The flow of direct noninterrupted currents of subthreshold intensity in the nodal regions produces important changes in the excitability of the adjoining tissues. These changes in the excitability may or may not be related to the "excitatory local process" described by Hodgkin. If the excitability increases, as happens after cathode current is applied, the electrotonic variations originated in the auricles may set up a focus in the nodal region or in the ventricles.

The effect produced by applying an electric current of subthreshold intensity is very similar to the effect caused by the current generated by a polarized surface at the boundary of active and resting muscle in the auricle even if the activation wave has not arrived at the node. Nevertheless, the latter develops an ectopic focus more easily since the density of the current is increasing from monent to moment. During all the time before the activation wave arrives at the node, into this structure will flow a current of subthreshold intensity originated in the auricle (electrotonic variation). With this theory it is not necessary to give explanations which look complicated.

After a lesion is produced in the bundle of His with the thermocautery, there is no doubt that, in the injured region and in the surrounding area, there is a diminution in conductivity, in the action potential, in the excitability and in the electrotonic variations, which easily explain why the Wolff-Parkinson-White syndrome does not develop.

The authors state that certain experiments conducted recently in their laboratory indicate that specific areas of the ventricles can be blocked by interrupting the branch of the bundle supplying them. The results obtained in another laboratory, by producing incomplete or complete block of the right or left branch, do not support this idea.

Neither is it correct to say that after premature activation of a limited area in the ventricle the activation in the rest of the heart is normal. The authors did not study the sequence of activation of the ventricles in their experimental cases of Wolff-Parkinson-White syndrome. In clinical electrocardiography, the precordial, epicardial, and intracavity tracings strongly suggest marked modifications in the process of activation during all the electrical systole and not only in the first part.

The aberrant ventricular responses which exist in cases with auricular fibrillation are more easily explained by incomplete block of the left bundle branch. It should be appreciated that in cases with incomplete left bundle branch block, produced by tapping with a probe the place where the branch begins to descend, there is an initial slurring very similar to that seen in Wolff-Parkinson-White syndrome. Recently in our laboratory, using intraseptal leads, it has been possible to understand the mechanism of this slurring.

I could discuss many other parts of the book, but I have limited myself to what I consider the most important. Notwithstanding these different points of view, the experiments related by the authors are good and the book should be read carefully by all of those interested in electrocardiographic problems. I wish that the authors had not published a book but instead that they had published an article since it is not possible to accept the main conclusions without further investigation.

D. S. P.

Announcements

Life Insurance Medical Research Fund
Research Fellowships and Grants

Applications for awards available July 1, 1953, will be received by the Life Insurance Medical Research Fund as follows: (1) Postdoctorial research fellowships, until Oct. 31, 1952. Preference is given to those who wish to work on cardiovascular function and disease or related fundamental problems. Stipends vary from $3,300 to $4,500. (2) Grants to institutions in aid of research on cardiovascular problems, until Nov. 15, 1952. Support is available for physiologic, biochemical, and other basic research on cardiovascular problems as well as for clinical investigation in this field. Further information and application blanks may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 2 East 103rd Street, New York 29, N. Y.

American Society for the Study of Arteriosclerosis: Program of the Sixth Annual Meeting, Hotel Knickerbocker, Chicago, Ill., Nov. 9-10, 1952.

Sunday, Nov. 9, 1952, A.M.

1. The Effect of Heparin and Other Agents on the Cholesterol Partition and Lipoprotein Pattern. C. Moses, G. L. Rhodes, and C. Wray, Addison H. Gibson Lab., Univ. Pittsburgh, Pa.
2. The Influence of Hormones on the Distribution of Lipoproteins in Plasma. D. P. Barr, E. M. Russ, and H. A. Eder, Dpt. Med., N. Y. Hosp., Cornell Med. Center, New York, N. Y.
3. A New and Simple Technique for Detecting Disturbances in the Serum Lipid Pattern in Health and Disease. L. Horlick, Dpt. Path., McGill Univ., Montreal, Canada.
4. Atherosclerosis: An In Vitro Study of the Nature of Atherogenesis. S. M. Evans, H. K. Ihrig, J. Menas, W. Zeit, R. N. Hazelwood, and E. R. Haushalter, Dpt. Med. & Anat., Marquette Univ., and Research Lab., Allis-Chalmers Mfg. Co., Milwaukee, Wis.
5. Foam-Cellular Lesions of the Aorta and Coronary Arteries of the Dog. L. L. Waters, Dpt. Path., Yale Univ., New Haven, Conn.
6. Atherosclerosis of the Carotid Arteries. C. M. Fisher, J. E. Pritchard, and W. H. Mathews, The Montreal Gen. Hosp., Montreal, Canada.
7. The Interaction of "Heparin Active Factor" and Lipoproteins. A. V. Nichols, N. K. Freeman, B. Shore, and L. Rubin, Div. Med. Physics, Donner Lab., Univ. Calif., Berkeley, Calif.
8. Serum Cholesterol Values in Men on Habitually Different Diets—Italy, Spain, England, and the United States. A. Keys, F. Fidanza, V. Scardi, G. Bergami, F. Vivance, C. J. Diaz, and J. T. Anderson, Lab. Physiol. Hygiene, Univ. Minn., Minneapolis, Minn.

Sunday, Nov. 9, 1952, P.M.

9. The Effect of Brain Extract on Blood Cholesterol and the Serum Lipid Pattern. R. B. Gordon, S. Kraft, and R. J. Jones, Dpt. Med., Univ. Chicago, Chicago, Ill.
10. Prevention of Hypercholesterolemia in the Rabbit—Successful Prevention of Cholesterol Atherosclerosis, Reduction of Blood Cholesterol in Man. O. J. Pollak, Dover, Del.
11. Age-Conditioned Spontaneous Regression of Atherosclerosis in the Cholesterol-Fed Chicks. S. Rodbard, R. Pick, C. Bolene-Williams, and L. N. Katz, Cardiovasc. Dpt., Med. Research Inst., Michael Reese Hosp., Chicago, Ill.

12. Estrogen-Induced Regression of Coronary Atherosclerosis in Cholesterol-Fed Chicks. R. Pick, J. Stamler, S. Rodbard, and L. N. Katz, Cardiovasc. Dpt., Michael Reese Hosp., Chicago, Ill.
13. Endocrine Influences on Serum Lipoproteins and Atherogenesis in Cholesterol-Fed Chicks. J. Stamler, R. Pick, L. N. Katz, L. Lewis, and I. H. Page, Cardiovasc. Dpt., Michael Reese Hosp., Chicago, Ill., and Cleveland Clinic Found. Research Div., Cleveland, Ohio.
14. The Degree of Coronary Atherosclerosis in Castrated Women. J. H. Wuest, T. J. Dry, and J. E. Edwards, Div. Med. & Sct. Path. Anat., Mayo Clinic, Rochester, Minn.
15. Digitonine Precipitation as a Method for Improving the Specificity of the Schultz Test. S. P. Kent, Dpt. Path., Med. Col. Ala., Birmingham, Ala.
16. Plasma Heparin and Atherosclerosis. H. Engelberg, Los Angeles, Calif.

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17. The Distribution of the Vasa Vasorum of Arteries. C. A. Woerner, Dpt. Anat., Univ., Louisville, Ky.
18. Histochemical Studies of 5-Nucleotidase Activity in Human Aortae. I. Age and Regional Variations. C. H. Lupton, Jr., E. M. Ethridge, and J. F. A. McManus, Dpt. Path., Univ. Va., Charlottesville, Va.
19. Pathologic Changes of Endothelium Demonstrated by Impregnation With Silver Nitrate. R. Altschul, Dpt. Anat., Univ. Saskatchewan, Saskatoon, Canada.
20. Surface Studies of the Early Development of Cholesterol Atherosclerosis in the Rabbit. E. V. Lautsch, G. C. McMillan, and G. L. Duff, Dpt. Path., McGill Univ., Montreal, Canada.
21. Histochemical Studies of the Early Lesions of Cholesterol Atherosclerosis in the Rabbit. I. Klatzo, G. C. McMillan, and G. L. Duff, Dpt. Path., McGill Univ., Montreal, Canada.
22. Factors Affecting the Distribution of Vascular Disease in Hypercholesterolemic Rabbits. G. M. Hass, F. B. Kelly, Jr., and C. B. Taylor, Rush Dpt. Path., Presbyterian Hosp., Chicago, Ill.
23. Arteriosclerosis in the Dog. A Comparison of Spontaneous and Experimental Lesions. S. Lindsay, and I. L. Chaikoff, Univ. Calif. School of Med., San Francisco, Calif.
24. Analysis of Aortic "Arteriosclerosis" in 300 Consecutive Autopsies. H. C. McGill, G. Peck, and R. L. Holman, Dpt. Path., La. State Univ. and Charity Hosp., New Orleans, La.

Monday, Nov. 10, 1952, P.M.

25. Relationships Between the Levels of Dietary, Liver and Serum Cholesterol and Hepatic Cholesterol Synthesis. I. D. Frantz, Jr., H. S. Schneider, and B. T. Hinkelman, Cardiovasc. Research Lab., Mass. Gen. Hosp., and Harvard Med. School, Boston, Mass.
26. Idiopathic Hypercholesteremia: Frequency in a Hospital Population and in the Families of Hypercholesteremic Index Patients. D. Adlersberg, S. R. Drachman, L. E. Schaefer, and A. G. Steinberg, Mt. Sinai Hosp., New York, N. Y.
27. Presenile Medial Calcinosis of the Arteries of the Extremities. N. W. Barker, H. L. Smith, and J. E. Edwards, Div. Med. & Sect. Path. Anat., Mayo Clinic, Rochester, Minn.
28. Cation Content of the Aorta Wall in Renal and DCA Hypertension. L. Tobian, Jr., and J. Binion, Dpt. Biol. Chem., Harvard Univ. Med. School, Boston, Mass.
29. Vascular Lesions Elicited by Renin in Nephrectomized Dogs. G. M. C. Masson, A. C. Corcoran, and I. H. Page, Research Div., Cleveland Clinic Found., Cleveland, Ohio.
30. Vascular Response in Local and Systemic Circulation to Various Sympatholytic and Vasodilator Drugs Following Peripheral Cold Injury. B. Jablons, and A. H. Wolfson, Goldwater Mem. Hosp., New York, N. Y.
31. The Effect of Aureomycin on Serum Lipids and Vascular Lesions in Cholesterol-Fed Rabbits. D. Nelson, R. Willheim, A. C. Ivy, and A. Altschul, Dpt. Clin. Sc., Univ. Ill., Chicago, Ill., and Dpt. Anat., Univ. Saskatchewan, Saskatoon, Canada.
32. The Effect of Cortisone and ACTH on Experimental Cholesterol Atherosclerosis in Rabbits. E. Oppenheim, and M. Bruger, Dpt. Med., N. Y. Univ., New York, N. Y.
33. Peripheral Neurectomy for Pain in Obliterative Arterial Disease. A. Blain, III, and F. S. Gerbasi, Alexander Blain Hosp., Detroit, and Univ. Mich., Ann Arbor, Mich.
34. Genetic Studies on Coronary Atherosclerosis Developing After Age 60. E. P. Boas, and D. Adlersberg, Mt. Sinai Hosp., New York, N. Y.
35. The Assay of Plasma Heparin, Using Anticoagulant Activity as a Measure of Heparin. L. Freeman, H. Engelberg, and A. Dudley, Cedars of Lebanon Hosp., Los Angeles, Calif.
36. The Effect of Choline on the Serum Cholesterol and Phospholipids in Patients With Coronary Artery Disease. S. U. Greenberg, and M. Bruger, N. Y. Univ., New York, N. Y.
37. Arteriosclerotic Popliteal Aneurysm: A Clinical and Follow-up Study. E. A. Hines, Jr., R. W. Gifford, Jr., and J. M. James, Div. Med., Mayo Clinic, Rochester, Minn., Sect. Orthop. Surg.

38. The Ratio Between Phospholipid and the Cholesterols of Blood as an Index of Human Atherosclerosis. R. S. Jackson, and C. F. Wilkinson, Jr., Dpt. Med., New York Univ., New York, N. Y.
39. Effect of Testosterone and Chorionic Gonadotrophin on Estrogen-Induced Inhibition of Coronary Atherogenesis in Cholesterol-Fed Cockerels. L. N. Katz, J. Stamler, R. Pick, and S. Rodbard, Cardiovasc. Dpt., Michael Reese Hosp., Chicago, Ill.
40. In Vitro Lipoprotein Transformations. F. T. Lindgren, N. K. Freeman, and D. M. Graham, Donner Lab., Univ. Calif., Berkeley, Calif.
41. The Results of Diet, Medicinal Agents and Emotional Disorders on Serum Phospholipid-Cholesterol Ratios in Coronary Atherosclerosis. L. M. Morrison, Los Angeles, Calif.
42. Studies on the Fate of C-14-Labeled Cholesterol and its Oxidation Products After Intravenous Injection. E. H. Mosbach, W. Meyer, and F. E. Kendall, Goldwater Mem. Hosp., New York, N. Y.
43. Analytical Comparison of Cholesterol, Phospholipids and Ratios. J. W. Perry, E. W. Townsend, and P. B. Roen, Hollywood Presbyt. Hosp., Los Angeles, Calif.
44. Influence of Gonadectomy on Cholesterol-Induced Aorta and Coronary Atherogenesis in Young Chicks. R. Pick, S. Rodbard, J. Stamler, and L. N. Katz, Cardiovasc. Dpt., Michael Reese Hosp., Chicago, Ill.
45. Prevention and Therapeutic Management of Atherosclerosis. P. B. Roen, E. E. Townsend, and J. W. Perry, Hollywood Presbyt. Hosp., Los Angeles, Calif.
46. Cholesterol, Antilipfanogen and Fat Deposition. H. S. Simms, R. B. Best, and C. R. Harminson, Columbia Univ., New York, N. Y.
47. Effects of Adrenal Steroid Compound F on Plasma Lipids and Atherogenesis in Cholesterol-Fed Chicks. J. Stamler, R. Pick, and L. N. Katz, Cardiovasc. Dpt., Michael Reese Hosp., Chicago, Ill.
48. The Effect of Estrogen on Serum Phospholipid. E. W. Townsend, J. W. Perry, and P. B. Roen, Hollywood Presbyt. Hosp., Los Angeles, Calif.
49. A Comparison of the Chylomicron Index, Serum Total Cholesterol and Lipid Phosphorus as Indices of an "Atherosclerotic State." W. J. Zinn, and G. C. Griffith, Dpt. Med., Univ. Southern Calif., Los Angeles, Calif.
50. Studies on the Mechanism of the Regression of Experimentally Produced Arterial Lesions in Dogs. M. Bevans, L. L. Abell, and F. E. Kendall, Goldwater Mem. Hosp., New York, N. Y.
51. The Effect of Heparin and Placebo Therapy in Coronary Artery Disease. H. Miller, W. J. Zinn, and G. C. Griffith, Dpt. Med., Univ. Southern Calif., Los Angeles, Calif.
52. Classification of Arteriopathies. J. B. Wolffe, Philadelphia, N. W. Barker, Rochester, Minn., A. C. Corcoran, Cleveland, Ohio, G. L. Duff, Montreal, Canada, and H. B. Sprague, Boston, Mass. Nomenclature Committee of the American Society for the Study of Arteriosclerosis.—To be discussed at the business meeting.